Impacto de la Ventilación Prolongada No Invasiva en Niños: Tendencias, Resultados y Adherencia

Long-term Non-invasive Ventilation in Children: Trends, Outcomes and Adherence

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Declaration

This thesis by compendium of articles is an original work. Data has been published in peer reviewed manuscripts and conference abstracts or is under peer review.

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and the opportunity

to become a good researcher, a brighter physician and a better person.

Resumen (versión en castellano)

La ventilación no invasiva (VNI) a través de una interfase externa a la vía aérea se ha convertido en una modalidad de asistencia respiratoria cada vez más frecuente en pediatría. Actualmente, el uso de VNI prolongada se considera la primera opción terapéutica en niños y niñas con trastornos de la respiración durante el sueño o insuficiencia respiratoria crónica. Desde los primeros estudios pediátricos sobre VNI publicados en la década de 1980, ha habido un creciente número de publicaciones relacionadas con el uso de VNI prolongada en pediatría. Sin embargo, existen lagunas en el conocimiento actual sobre el uso y los beneficios de la VNI prolongada en pediatría, incluyendo la falta de revisiones sistemáticas que resuman la literatura existente en este tema, los cambios en el perfil de los niños y niñas que reciben VNI y la falta de datos sobre resultados clínicos de la VNI a largo plazo.

La primera parte de esta tesis, presentada en los capítulos 2 y 3, informa sobre los métodos y resultados de una revisión sistemática exploratoria de la literatura ("scoping review", en inglés) en el uso de VNI prolongada en pediatría. El objetivo principal de este estudio se centra en proporcionar una visión global de la literatura primaria existente relevante al uso de VNI prolongada en pediatría, identificar áreas específicas con suficiente literatura como para llevar a cabo una revisión sistemática adicional y metaanálisis, y determinar las limitaciones del conocimiento actual que puedan determinar futuras líneas de investigación. Se han utilizado nuevos métodos de revisión sistemática exploratoria que incluyeron un proceso de consulta de expertos y priorización de términos de inclusión en la búsqueda bibliográfica y el desarrollo de un protocolo riguroso de identificación de literatura científica (publicada y no publicada) relevante en el uso de VNI prologada en pediatría en múltiples fuentes

bibliográficas, con el objetivo de presentar una panorámica completa en este tema. Se seleccionaron 11 581 estudios de los cuales se incluyeron 289. Los resultados de este estudio han identificado 76 términos diferentes utilizados en referencia a VNI, siendo "ventilación no invasiva (NIV, por sus términos en inglés)" el término más utilizado. Asimismo, la metodología de la gran mayoría de los estudios incluidos fue de baja calidad y alto riesgo de sesgo. La síntesis de datos identificó el uso de VNI prolongada en 73 patologías diferentes, siendo la apnea obstructiva del sueño (29%) y atrofia muscular espinal (8%) las más frecuentemente estudiadas. Los resultados fueron exclusivamente descriptivos (p. ej., características clínicas del paciente, tecnología utilizada, descripción de resultados clínicos sin grupo control) en la gran mayoría de los estudios incluidos. Otros variables estudiadas fueron parámetros procedentes de estudios de sueño y parámetros no estandarizados de reducción de morbilidad respiratoria (27% y 19% de los estudios, respectivamente), los cuales difirieron según el grupo diagnóstico. En general, los resultados de esta revisión ponen de relieve la existencia de una gran cantidad de publicaciones sobre el uso de la VNI prolongada en pacientes pediátricos en una gran diversidad de patologías subyacentes. Sin embargo, la mayoría de los estudios han sido de naturaleza observacional y descriptiva, con una clara carencia de estudios con mayor calidad metodológica que incluya variables estandarizadas y mayor orientación hacia al paciente. Además, aunque existe mucha información en niños y niñas con ciertas patologías, hay escasos datos relevantes para muchas otras subpoblaciones pediátricas. Añadido a todo esto, las variables evaluadas a menudo se centran en parámetros que pueden no ser los más relevantes para los niños y niñas que usan VNI ni para sus familias.

La segunda parte de esta tesis, incluida en los capítulos 4 y 5, presenta los resultados de un estudio de cohortes multicéntrico de niños y niñas que iniciaron VNI prolongada en la provincia de Alberta (Canadá) durante el período 2005-2014. El estudio fue diseñado como un estudio poblacional ya que solo hay dos laboratorios de sueño financiados con fondos públicos afiliados a las dos clínicas pediátricas de VNI en centros de atención terciaria en la provincia y, por tanto, incluye a la mayoría (sino a todos) los niños y niñas que usan VNI en esta zona.

El Capítulo 4 describe los cambios observados en la población pediátrica que recibe con VNI en la provincia durante una década, incluyendo los cambios en prevalencia e incidencia del uso de VNI prolongada, así como los cambios en la tecnología utilizada, las características clínicas iniciales de dicho grupo y su progresión clínica. Los datos se dividieron en tres períodos de tiempo iguales y no superpuestos (2005-2008; 2008-2011; 2011-2014). En el periodo estudiado, se inició VNI prolongada en 622 pacientes. La incidencia y prevalencia de uso de la VNI se quintuplicaron de 2005-2008 a 2008-2011, y triplicaron de 2008-2011 a 2011-2014. Respecto a sus características clínicas, es de destacar el incremento en el uso de VNI prolongada en niños y niñas con enfermedades neurológicas y cardiorrespiratorias, pero no se detectaron cambios en su complejidad médica o en la gravedad del trastorno respiratorio subyacente. En general, la supervivencia fue del 95%. Sin embargo, la tasa de mortalidad aumentó de manera alarmante de 3,4 casos por 1000 niño/a-año en 2005-2008 a 142,1 en el último periodo de 2011-2014. El análisis de subgrupos mostró diferencias en la tasa de mortalidad según el grupo diagnóstico, con curvas de supervivencia más bajas y tasas de mortalidad más altas en niños y niñas con enfermedades neurológicas y cardiorrespiratorias. En conjunto, los resultados demuestran no solo un mayor uso de la VNI prolongada en pediatría a

lo largo del tiempo, sino también un cambio en las patologías subyacentes como causa de indicación de la VNI, y un aumento alarmante en la tasa de mortalidad que quizás puede atribuirse al mayor uso de la VNI en niños y niñas con enfermedades neurológicas y cardiorrespiratorias.

El capítulo 5 presenta los resultados del análisis longitudinal retrospectivo que describe los cambios a lo largo del tiempo en cuanto a la eficacia de la VNI (cambios en variables polisomnográficas respiratorias y de sueño y en el índice de masa corporal), adhesión al tratamiento y tasa de complicaciones en la misma cohorte de niños y niñas con VNI prolongada. Se utilizaron modelos de efectos mixtos para analizar los datos de 429 pacientes con suficientes datos para su inclusión en el estudio. Este trabajo demostró mejoras significativas en todos los parámetros respiratorios y de sueño recogidos en los estudios polisomnográficos de sueño tras el inicio de la VNI, incluyendo: mayor eficiencia del sueño, menor número de despertares, reducción del índice de apnea-hipopnea y mejora en el intercambio de gases. No solo se demostró que la VNI es eficaz si no también que su eficacia se mantiene en el tiempo. Los cambios en el hábito corporal, sin embargo, difirieron según el índice de masa corporal al comienzo de la aplicación de la VNI. Si bien niños y niñas con peso normal experimentaron un aumento significativo de su índice de masa corporal (z-score) de 0,11 por año de VNI, este aumento fue 3 veces mayor en niños y niñas con bajo peso, logrando la normalización de su indicie de masa corporal en los primeros 12 meses de terapia de VNI. No hubo cambios significativos en el índice de masa corporal en niños y niñas con sobrepeso. Sin embargo, niños y niñas con obesidad redujeron su índice de masa corporal (z-score) en 0,15 por año de VNI. La adhesión al tratamiento mejoró a lo largo del tiempo, con un aumento del 4% en el porcentaje

de días al mes con uso de VNI por encima de las 4 horas y con 19 minutos extra de uso nocturno por cada año de VNI, mientras que la tasa de complicaciones se mantuvo baja y estable en el tiempo. En resumen, nuestro análisis longitudinal concluye que la VNI prolongada es una terapia eficaz con beneficios generales mantenidos en el tiempo en los parámetros de sueño y respiración durante el sueño, una mejora de la adhesión al tratamiento y una tasa baja de complicaciones a lo largo del periodo de seguimiento. Sin embargo, los posibles beneficios de la VNI prolongada en el hábito corporal difieren según el índice de masa corporal inicial, con beneficios notables en poblaciones pediátricas con bajo peso y obesidad. En conjunto, estos resultados demuestran los beneficios de la VNI en poblaciones pediátricas, así como la reducción progresiva de las posibles cargas asociadas al tratamiento.

En conjunto, estos proyectos han contribuido a mejorar el conocimiento sobre el uso de la VNI prolongada en pediatría. Si bien los resultados de nuestra revisión sistemática exploratoria muestran una panorámica rigurosa de la literatura existente y destacan las brechas relevantes en el conocimiento, este trabajo ha contribuido a establecer un contexto en el que construir una agenda de investigación, incluyendo la necesidad urgente de desarrollar registros grandes de niños y niñas con VNI prolongada y estudios multicéntricos de alta calidad metodológica, un mayor esfuerzo en la identificación de variables clínicas de interés para el paciente y una revisión sistemática adicional en áreas más específicas identificadas en este trabajo. Algunas de las áreas interesantes para llevar a cabo revisiones sistemáticas adicionales y metaanálisis incluyen: 1) supervivencia y otras variables clínicas relevantes en poblaciones pediátricas con trastornos neuromusculares tratados con VNI prolongada. 2) Adhesión al tratamiento de VNI prolongada en pediatría. 3) Cambios en el hábito corporal y otros

parámetros metabólicos en niños y niñas con obesidad y trastornos de la respiración durante el sueño tratados con VNI. Además, nuestro análisis poblacional ha demostrado cambios importantes en el uso de la VNI en pediatría a lo largo del tiempo, lo que refuerza la necesidad de futuros estudios prospectivos que incorporen marcos relevantes de complejidad médica y analicen los patrones de mortalidad para poder comprender mejor estas tendencias. Finalmente, nuestro análisis longitudinal es novedoso al demostrar beneficios de la VNI prolongada en el crecimiento en niños y niñas con bajo peso u obesidad, y justifica la necesidad de estudios prospectivos adicionales que evalúen el efecto de la VNI prolongada, sola o en combinación con otras terapias médicas y cambios en estilo de vida, en el hábito corporal, el crecimiento y otros parámetros metabólicos.

Esperamos que estos resultados sean útiles para profesionales de la salud que atiendan a niños y niñas tratados con VNI prolongada y que ayude a diseñar futuras investigaciones que traten de rellenar las lagunas del conocimiento aquí identificadas.

Abstract (English version)

Non-invasive ventilation (NIV) in children has become an increasingly common modality of breathing support delivered through an interface outside of the airway. At this time, the use of long-term NIV is considered a first-line option for many children with impaired breathing during sleep and chronic respiratory insufficiency or failure. Since the first reports of NIV use published in children in 1980's, there has been a growing body of the literature related to the use of long-term NIV in children. However, there are gaps in our present knowledge on the use and benefits of long-term NIV in children including lack of reviews using systematic methods to summarize the existing literature on this topic, changes in the profile of children receiving NIV, and lack of data related to long-term outcomes.

The first part of this thesis, presented in chapters 2 and 3, reports on the methods and results of a scoping review in the use of long-term NIV in children. This study aimed to provide an overview of the existing primary research relevant to long-term NIV use in children, identify data appropriate for systematic review, and highlight gaps in current knowledge. We followed rigorous, recently developed methodology including expert consultation and prioritization of 'terms' for search strategy and the design of a protocol to identify all relevant literature (published and unpublished) to define the full scope of current knowledge on long-term NIV use in children. We screened 11,581 studies with final inclusion of 289. The results identified 76 different terms used to refer to the concept of NIV with the most commonly used term being 'non-invasive ventilation (NIV)'. The vast majority of studies were of low methodological quality. The data synthesis identified use of long-term NIV across 73 different medical conditions with obstructive sleep apnea (29%) and spinal muscular atrophy (8%) being the most

common individual conditions. The most commonly reported outcomes were descriptive (e.g. patient characteristics, NIV technology used, description of outcomes without control group) with reporting of sleep studies and non-standardized parameters to measure reduction in respiratory morbidity reported less often (27% and 19% of studies respectively). Reported outcomes of interest differed by diagnostic category. Overall, the results of this scoping review highlight there is a large body of literature in the use of long-term NIV in children with a great diversity of underlying conditions. However, most studies have been observational and descriptive in nature, with a clear lack of rigorously designed studies. Further, while more robust information exists for some conditions, there is scarce data relevant to many other pediatric subpopulations. In addition, outcomes studied may not be those of highest priority for children using NIV and their families.

The second part of this thesis, presented in chapters 4 and 5, reports the results of a multicenter cohort study of children initiated on long-term NIV in the province of Alberta for the period 2005-2014. The study was design as a population study as there are only two publicly funded sleep laboratories affiliated with the two tertiary care pediatric NIV clinics in the province and, therefore, includes most if not all children on NIV.

Chapter 4 reports on the longitudinal trends in NIV initiation, as well as clinical characteristics, NIV technology use and outcomes in children using long-term NIV over a decade. The data was divided in three equal and non-overlapping time periods (i.e. 2005-2008; 2008-2011; 2011-2014) and included 622 children. The results showed an increase in NIV incidence and prevalence of five and three fold respectively over the 10-year period. More

children with neurological and cardio-respiratory conditions started NIV over time but neither medical complexity nor severity of the underlying sleep-related breathing disorder changed over time. Overall, survival was 95%. The mortality rate, however, increased over time from 3.4 cases to 39.2 and 142.1 per 1000 children-years between 2005-2008 and 2011-2014 respectively. Subgroup analysis showed that mortality rates differed by diagnostic category, with lower survival curves and higher mortality rates in children with neurological and cardio-respiratory conditions. Together, the results demonstrate not only a higher long-term NIV use in children over time, but also a change in the underlying conditions leading to NIV initiation, and an alarming increase in mortality rate maybe attributable to increased use of NIV in children with neurological and cardio-respiratory conditions.

Chapter 5 presents the results of the analysis of longitudinal clinical outcomes including the efficacy of NIV (respiratory and sleep polysomnographic parameters, and changes in body mass index), and changes in NIV adherence and complication rate over time for the same cohort of children. Mixed effects models were used to analyze the data from 429 children with sufficient data for inclusion. The findings of this study showed that sleep parameters, apnea-hypopnea index, and gas exchange improved after NIV initiation and that these improvements were sustained over time. Change in body habitus over time, however, differed by body mass index at NIV initiation. While body mass index z-score in normal weight children increased by 0.11 per year on NIV, this increase was 3-fold higher in underweight children, with normalization of body habitus within the first 12 months. There was no change in body mass index for overweight children and dropped by 0.15 per year on NIV in obese children. Adherence improved, with a 4% increase in the percentage of days with NIV use above 4 hours

in a month and 19 extra minutes of night use for each year of NIV therapy, while complication rate remained low and stable over time. In summary, our longitudinal analysis concludes that long-term NIV is an efficacious therapy with overall sustained benefits on sleep and breathing parameters and improved adherence over time. Its benefits on body habitus, however, differ by initial body mass index group, with remarkable benefits in underweight and obese children. Overall, these results demonstrated the long-term benefits of NIV in children as well as the progressive reduction of the potential burden treatment over time.

Together, these projects have contributed to improve the knowledge on the use of long-term NIV in children. While the results of this scoping review provide a rigorous overview of the existing literature and highlights relevant gaps in knowledge, this work has contributed to set a context on which to build a research agenda including the urgent need for the development of large registries of children using NIV and multicenter high-quality studies, research around patient-oriented outcomes and further systematic review in suggested areas such as outcomes of NIV in children with neuromuscular disorders, adherence to NIV in children, or changes in growth and metabolic outcomes in obese children using NIV. Further, our trend analysis has demonstrated dramatic changes in the use of NIV in children over time that reinforced the need for further prospective large studies that incorporate relevant frameworks for medical complexity and further analyze mortality patterns to better understand these trends. Finally, our longitudinal analysis is novel at demonstrating long-term benefits in growth in underweight and obese children and justifies the need for further prospective studies assessing the long-term effect of NIV alone or in combination with other medical therapies and lifestyle changes in growth and metabolic outcomes. It is our expectation that these results are useful for health

care professionals and stakeholders taking care of children using long-term NIV, allow them to better plan for the care of this group and help establish a future research agenda in keeping with the gaps identified and not fulfilled through this work.

Preface and Contributions

The following manuscripts comprises this thesis by compendium of articles and have been published or are under review as:

1. ***Castro Codesal ML**, Featherstone R, Martinez Carrasco C, Katz SL, Chan EY, Bendiak GN, Almeida FR, Young R, Olmstead D, Waters KA, Sullivan C, Woolf V, Hartling L, MacLean JE. Long-term noninvasive ventilation therapies in children: a scoping review protocol. BMJ Open 2015; 5: 8 e008697. DOI: 10.1136/bmjopen-2015-008697 (IF 2.413).* This manuscript is included in chapter 2. For the development of this project, MLCC and JEM initially conceptualized the study and acquired funding. MLCC, RF, LH, and JEM participated in the idea of this study and designed its methodology. MLCC wrote the protocol, developed the search strategy and performed a preliminary literature review. RF assisted with the development of the search strategy and preliminary literature review. MLCC, KAW, CMC, SLK, EYC, GNB, CS, FRA, RY, DO, VW, LH, JEM participated in the design of the methods and reviewed the final version of the protocol. MLCC collected comments from authors and wrote the initial draft of the manuscript. All authors read and approved the final manuscript. The overall supervision of the study was done by JEM.
2. ***Castro Codesal ML**, Dehaan K, Featherstone R, Martinez Carrasco C, Katz SL, Chan EY, Bendiak GN, Almeida FA, Olmstead D, Young R, Woolf V, Waters KA, Sullivan C, Hartling L, MacLean JE. Long-term non-invasive ventilation therapies in children: a scoping review. Sleep Med Rev 2017; 37: 148-158. DOI: 10.1016/j.smrv.2017.02.005. (IF 10.342).* This manuscript is included in chapter 2. MLCC and JEM initially conceptualized the

study and acquired funding. MLCC, RF, LH and JEM participated in the idea of this study and designed the methodology. KAW, CMC, SLK, EYC, GNB, CS, FRA, RY, DO, and VW reviewed and provided suggestions on the methods. RF conducted the literature searches and developed the endnote libraries. MLCC, JEM screened all records and compared libraries. MLCC conducted the search of grey literature and MLCC and JEM reviewed included records from grey literature. MLCC, KD and PB performed the data extraction of included records with contributions from SLK, GNB, EYC, RY, DO, JEM. MLCC analyzed the data. MLCC and JEM interpreted the data and developed the framework for data synthesis. MLC and JEM undertook the update of the literature search with the assistance of RF. MLCC wrote the initial draft of the manuscript. All authors reviewed the manuscript and approved the final version. The overall supervision of the study was done by JEM.

3. ***Castro-Codesal ML**, Dehaan K, Bedi PK, Bendiak GN, Schmalz L, Katz SL, MacLean JE. Long-term non-invasive ventilation in children: regional longitudinal trends and outcomes. PLoS One 2018; 13: 1 e0192111. DOI: 10.1371/journal.pone.0192111. eCollection 2018 (IF 2.768).* This manuscript comprises chapter 3. MLCC and JEM initially conceptualized the study and acquired funding. MLCC, GNB, LS, and SLK participated in the study. MLCC undertook the data curation with the collaboration of KD, PKB and JEM. MLCC analyzed the data. Dr. Jesus Serrano-Lomelin gave special knowledge for the statistical analysis. MLCC and JEM interpreted the data. MLCC wrote the initial draft of the manuscript. All authors reviewed the manuscript and approved the final version. The overall supervision of the study was done by JEM.

4. ***Castro-Codesal ML**, Dehaan K, Bedi PK, Bendiak GN, Schmalz L, Rosychuk RJ, MacLean JE. Long-term improvements in sleep, breathing, and adherence in children on long-term non-invasive ventilation.* In review by to Canadian Journal of Respiratory, Critical Care and Sleep Medicine (January 2019). This manuscript is included in chapter 4. MLCC and JEM conceptualized the work with participation of GNB. MLCC, KD, PKB, GNB, and LS collected or facilitated collection of the data. MLC, RJR and JEM designed the data analysis. MLCC analyzed the data. MLCC, RJR, and JEM interpreted the data. MLCC was responsible for drafting of the initial manuscript. KD, PKB, GNB, LS, RJR, and JEM critically appraised the manuscript. All authors approved the final version and are accountable for the work.

Work related to this study

Peer review manuscripts

1. Bedi P, **Castro-Codesal M**, Dehaan K, MacLean JE. The use and outcomes of long-term non-invasive ventilation for infants. Canadian Journal of Respiratory, Critical Care and Sleep Medicine 2018. DOI: 10.1080/24745332.2018.1465369 (IF NA).
2. Bedi P, **Castro-Codesal M,** Featherstone R, Albalawi MM, Kozyrskyj AL, Flores-Mir C, MacLean JE. Long-term non-invasive ventilation in infants: A systematic review and meta-analysis. Front Pediatr 2018; 6: 13. DOI: 10.3389/fped.2018.00013. eCollection 2018 (IF 2.172).

Publications-abstracts

First author:

1. **Castro-Codesal M**, Bedi P, Bendiak G, Schmalz L, Katz S, MacLean JE. Longitudinal Changes in Clinical Characteristics and Outcomes for Children Using Long-Term Non-Invasive Ventilation. American Journal of Respiratory & Critical Care Medicine 2018; 197: A2055.
2. **Castro Codesal M**, DeHaan K, Featherston R, Bedi P, Carrasco CM, Katz SL, Chan EY, Bendiak GN, Almeida FR, Olmstead D, Young R, Woolf V, Waters KA, Sullivan C, Hartling L, MacLean JE**.** Long-term non-invasive ventilation therapies in children: a scoping review. Sleep 2017; 40: A329.
3. **Castro-Codesal M**, Bedi P, Olmstead D, Bendiak G, Katz G, MacLean JE. Outcomes and complications of long-term non- invasive ventilation in children In Alberta: 2003- 2014. Sleep 2015; 38: A351.

4. **Castro-Codesal M**, Bedi P, Olmstead D, Bendiak G, Katz S, MacLean JE. Trends and learning curve for pediatric home ventilation programs In Alberta: 2003-2014. Sleep 2015; 38: A351.
5. **Castro M**, Bedi P, Olmstead D, Bendiak G, Katz S, MacLean J. Long-term noninvasive ventilation: Trends of the home ventilation programs in Alberta (2003-2014). Can Respir J Vol 22 Suppl A April 2015: 24A.
6. **Castro M**, Bedi P, Olmstead D, Bendiak G, Katz S, MacLean J. Long-term noninvasive ventilation in Alberta (2003-2014): Outcomes and Complications. Can Respir J Vol 22 Suppl A April 2015: 24A.

Co-author:

1. Gerdung C, **Castro-Codesal M**, Nettle-Aguirre A, Kam K, Hanly P, Maclean J, Bendiak G. Use of Split-Night Polysomnography in Children with Sleep Disordered Breathing. Sleep 2018;41 Suppl 1:A281.
2. Al-khaledi B, Olmstead D, Bedi P, Sebanstianski M, Featherstone R, Al-balawi MM, **Castro-Codesal ML**, MacLean JE. A systematic review of adherence to long-term non-invasive ventilation in children. Sleep 2017; 40: A348.
3. Al-balawi MM, **Castro-Codesal ML**, Featherstone R, Sebanstianski M, Al-khaledi B, Bedi P, MacLean JE**.** A systematic review of health outcomes for children with neuromuscular disorders using long-term non-invasive ventilation. Sleep 2017; 40: A321.
4. Wollin D, **Castro Codesal ML**, DeHaan K, MacLean JE. Characterizing treatment emergent central sleep apnea in children. Sleep 2017; 40: A320.

5. Bedi PK, DeHaan K, Castro-Codesal M, **MacLean JE**. The use and outcomes of long-term non-invasive ventilation in infants. American Journal of Respiratory & Critical Care Medicine 2017; 195: A4105

Scientific presentations (invited speaker)

1. Long-Term Benefits in Sleep, Breathing and Growth and Changes in Adherence in Children on Non-Invasive Ventilation. Alberta Research Centre Seminar, Edmonton, AB, Canada. Scheduled April 2019.
2. Longitudinal changes in characteristics and outcomes of children receiving long-term NIV. Alberta Research Centre Seminar, Edmonton, AB, Canada. April 2018.
3. Long-term non-invasive ventilation: options, methods and surveillance in Alberta. Canadian Respiratory Conference, Halifax, NS, Canada. April 2016.

Scientific oral presentations (peer reviewed)

First author:

Castro Codesal M, Dehaan K, Featherstone R, Hartling L, MacLean JE. Long-term non-invasive ventilation in children: scoping review. Pediatric Research Day, University of Alberta, Edmonton, AB. May 2016.

Co-author:

Bedi P, **Castro M**, MacLean JE. Long-term non-invasive ventilation in children in Alberta (2002-2014): clinical course and outcomes of the Edmonton cohort. Women and Children's Health Research Institute Research Day, University of Alberta, Edmonton, AB. November 2014.

Scientific poster presentations (peer reviewed)

First author:

1. **Castro-Codesal M**, Bedi P, Bendiak G, Schmalz L, MacLean JE. Long-Term Benefits in Sleep, Breathing and Growth and Changes in Adherence in Children on Non-Invasive Ventilation. Canadian Respiratory Conference, Ottawa, ON, Canada. April 2019 (pending for publication).
2. **Castro Codesal M**, DeHaan K, Featherston R, Bedi P, Carrasco CM, Katz SL, Chan EY, Bendiak GN, Almeida FR, Olmstead D, Young R, Woolf V, Waters KA, Sullivan C, Hartling L, MacLean JE**.** Long-term non-invasive ventilation therapies in children: a scoping review. Canadian Sleep Society Conference, Calgary, AB, Canada. April 2017.
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4. **Castro Codesal M**, DeHaan K, Bedi P, Olmstead D, Bendiak G, Katz S, MacLean JE. Pediatric home ventilation programs in Alberta 2003-2014: Trends and learning curve. Pediatric Research Day, University of Alberta, Edmonton, AB, Canada. May 2015.
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Grants and awards

1. Project name: Pediatric long-term noninvasive ventilation in Alberta: 10-year experience.

   Role: principal applicant.

   Supervisor: Joanna MacLean.

   Funding agency: Respiratory Health Strategic Clinical Network mini-Grant 2015.

   Amount: $ 2,500.

   Duration: 12 months.

2. Project name: Long-term non-invasive ventilation in children in Alberta 2005-2014.

   Principal investigator: Maria Castro.

   Supervisor: Joanna MacLean.

   Funding agency: Pulmonary Research Group collaborative Grant 2015, University of Alberta.

   Amount: $ 3,000.

   Duration: 12 months.

3. Project name: Long-term non-invasive ventilation in children in Alberta.

   Role: co-investigator.

   Supervisor: Joanna MacLean.

   Funding agency: Women's and Children's Health Research Institute resident Grant 2015.

   Amount: $ 2,500.

   Duration: 24 months.

4. Project name: Long- term Non-invasive Ventilation in Children in Alberta (2003- 2014):

   Trends, outcomes and Complications

   Role: principal applicant.

Supervisor: Joanna MacLean.

Funding agency: WCHRI travel funding 2015.

Amount: $ 750.

Duration: 12 months.

5. Project name: Pediatric Long- Term Non-invasive Ventilation Support in Alberta: A 10-year Experience Exportable across Canada.

   Role: Principal Applicant.

   Mentor: Joanna MacLean.

   Funding agency: Stollery Children's Foundation Research Fellowship Grant 2014.

   Amount: $ 76,000 (salary support).

   Duration: 12 months.

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AHI Apnea hypopnea index

AT Adenotonsillectomy

ATS American Thoracic Society

AVAPS Average volume-assured pressure support

BMI Body mass index

BPAP Bilevel positive airway pressure

Cardio-Resp Cardio-Respiratory

CCHS Congenital central hypoventilation syndrome

CI Confidence interval

CNS Central nervous system

CO_2 Carbon dioxide

CPAP Continuous positive airway pressure

DMD Duchenne muscular dystrophy

$ETCO_2$ Entidal carbon dioxide level

EPAP Expiratory positive airway pressure

FEV_1 Forced expiratory volume within the first second

IMV Invasive mechanical ventilation

IPAP Inspiratory positive airway pressure

MSNM Musculoskeletal and neuromuscular

NIV Non-invasive ventilation

NMD Neuromuscular disorders

NPV Negative pressure ventilation

OSA Obstructive sleep apnea

PAP Positive airway pressure

PCO_2 Carbon dioxide partial pressure

PG Polygraphy

PSG Polysomnography

REM Rapid eye movement

SD Standard deviation

SDB Sleep disordered breathing

SMA Spinal muscular atrophy

SpO2 Oxygen saturation by pulse oximetry

$TcCO_2$ Transcutaneous carbon dioxide level

Ti Inspiratory time

UA Upper airway

3D 3 dimensioning

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CHAPTER 1: REVIEW OF THE LITERATURE, AIMS AND HYPOTHESIS

Long-term mechanical ventilation has evolved since it was first introduced to clinical care almost 100 years ago. Today, non-invasive ventilation (NIV) is accepted as first line therapy for a range of disorders affecting breathing in children. This includes disorders affecting central respiratory control, upper airway patency, respiratory muscle function, lung function, as well as those with multiple respiratory pathologies. Understanding the interaction between the pathophysiology of the children using NIV and the NIV technology is paramount to optimizing the use of these therapies and the health outcomes of children using long-term NIV, preventing complications, and contributing to good adherence.

1.1. HISTORICAL PERSPECTIVE

1.1.1. Historical perspective of mechanical ventilation

Mechanical ventilation is a term used to describe any method of artificial breathing that employs mechanical or non-mechanical methods to move air into or out of the lungs. There are three main forms of mechanical ventilation: negative pressure ventilation, invasive tracheal ventilation, and non-invasive ventilation (NIV). Different modes of mechanical ventilation have dominated different periods in history and adapted to the medical needs of the time.

The clinical use of negative pressure ventilation started in the 1920s, with the development of the “iron lung”. This tank-like structure surrounded the user and connected to a pump that provided artificial respiration through the administration of negative pressure around the outside of the chest (1, 2). It was widely used in Europe and the US during the

poliomyelitis epidemics after the First World War, between 1930 and 1950 (3). It was comprehensively described during the polio outbreak in Denmark in 1952 (4); patients were kept inside the big iron tanks and confined to hospitals for long periods of time (Figure 1.1). The iron lung saved thousands of lives but carried a high personal and governmental cost. Practical limitations included: 1) insufficient number of iron lungs available; 2) inefficiency during the acute phase of the disease; 3) inadequate care of patients with bulbar involvement; and 4) complications arising from negative pressure, including diaphragm fibrosis, muscle atrophy related to the motion restriction, airway obstruction, and limitation of venous return (5). These problems resulted in a very high mortality rate (6, 7).

As an alternative to negative pressure ventilation, positive pressure ventilation via endotracheal tube or tracheostomy was then developed to control breathing in patients unable to generate a respiratory rate, protect their airway, or manage secretions, leading to the development of the modern intensive care units in the 1950s (4, 8). This form of mechanical ventilation applied positive pressure into the airways through an endotracheal or tracheostomy tube, alternating a high and low pressure to provide partial or full ventilation. For polio patients, the use of tracheal ventilation resulted in a drastic decline in mortality rates from approximately 70% to 17% (9). Therefore, there was a clear switch to a more efficient and affordable mode of respiratory support with positive pressure ventilation delivered via the trachea, with further development of home ventilators during the next several years. Although a few negative pressure devices were developed for home use (i.e. cuirass and negative pressure jackets), this mode of ventilation essentially disappeared.

1.1.2. Historical perspective of non-invasive ventilation

Interestingly, the development of NIV overlapped with the creation of the first positive and negative pressure ventilators (Figure 1.2). Since then, use of NIV has continued to grow, resulting in a subsequent reduction in the use of other forms of ventilation. In the mid-20th century, in adults and children with acute respiratory failure, positive pressure ventilators were used to apply two-level pressure ventilation through a mask connected to a ventilator by a double limb (one for inhalation and one for exhalation) (1). In the early 1970's, continuous positive airway pressure (CPAP) was first used during the resuscitation of newborns with neonatal respiratory distress syndrome and following cardiac surgery (10). The change from hospital to home-based NIV therapies occurred later, with the first cases of long-term NIV use in children with severe obstructive sleep apnea (OSA) published ten years later (11-13). Currently, long-term NIV is a plausible option for home mechanical ventilation in children, becoming the first line therapy for a range of disorders affecting breathing and breathing during sleep. Although tracheal ventilation can also be used at home, it requires a higher level of care and has been relegated to a second-line therapy when NIV does not sufficiently support ventilation or when the airway cannot be protected. The use of negative pressure ventilation is uncommon, being mostly testimonial with no substantial new research published.

1.2. FACTORS CONTRIBUTING TO THE INCREASED USE OF NON-INVASIVE VENTILATION IN CHILDREN

The use of NIV in children has expanded worldwide, including developing countries. This has resulted in a proportional decrease or stabilization in the use of invasive tracheal ventilation despite increasing numbers of children who survive critical illnesses and require respiratory support (14-27). Several factors may have contributed to this increase in NIV use (28-30). A growing number of children with critical medical conditions are now surviving early life but with significant sequelae that require a more complex level of care, including respiratory support. In addition, there has been a shift in the healthcare system from acute hospital-based care to a more chronic home-based model. This shift has resulted in a change in the burden of care to families as an alternative that allows children to live at home. At the same time, healthcare costs are reduced in this growing cohort of medically complex children (31-35). An increasing recognition of disorders affecting breathing during sleep or disorders initially impacting breathing during sleep, such as OSA and neuromuscular disorders (NMD), has resulted in a greater awareness of the potential benefits from long-term NIV (36, 37). Finally, technological advances in machines and mask interfaces have allowed home-based NIV therapies for children, even at very young ages (38, 39). These changes have likely contributed to NIV being considered the first line option of breathing support for chronic respiratory insufficiency or failure associated with a wide range of respiratory and sleep disorders, when intermittent time off respiratory support is possible (such as NIV for sleep only), or as part of palliative care (40, 41).

1.3. PATHOPHYSIOLOGY OF BREATHING ABNORMALITIES AND INDICATIONS FOR LONG-TERM NON-INVASIVE VENTILATION IN CHILDREN

NIV may be indicated in children with conditions that cause impairment in one or more of the physiological mechanisms of breathing, which include the central nervous system (CNS) control of breathing, upper airway patency, respiratory muscle function, and gas exchange. When one mechanism fails, compensation by other mechanisms may occur and if so, ventilation may be maintained until a certain threshold. Beyond that, ventilation becomes impaired resulting in hypoxemia and/or hypercapnia.

1.3.1. Impairment of breathing control

Conditions affecting the central drive to breath cause a reduction in the signal to the respiratory muscles resulting in impaired ventilation. Breathing begins in clusters of neurons in the brainstem that generate the breathing patterns (rhythm generator), with modulation of this pattern by other group of neurons that regulate the inspiratory, expiratory and post-expiratory phases. This breathing control system receives input from a system of receptors found at different levels of the respiratory system, which provide feedback through changes in pH and oxygen levels as well as mechanoreceptors in the airway and chest wall (42, 43). While central chemoreceptors located in the brainstem respond to changes in acid-base balance, peripheral chemoreceptors located at the carotid bifurcation are the major oxygen sensing cells, with more limited role in sensing changes in pH (44, 45). To some degree, this system for breathing control can be overridden by other anatomic centers located in the cerebellum, premotor areas, and motor cortex allowing voluntary control of breathing, to allow safe swallowing, and

speaking. Overall, the breathing control system maintains homeostasis by integrating anatomic, metabolic and mechanical input in the spinal motor neurons and sending signals through the vagal and glossopharyngeal nerves to activate upper airway and respiratory muscles. Then, it adjusts breathing to adapt to different physiological demands such as rest, exercise and sleep. During sleep, voluntary breathing control is absent and movement is absent or reduced so inputs to the respiratory centers are reduced (46); this explains why sleep can often unmask challenges to breathing, both from central and other causes, that are not apparent during wakefulness.

It is important to understand the developmental changes in sleep and breathing control when assessing concerns with breathing in early life. Control of breathing starts prenatally and continues to mature over the first months of life, with a critical period in the months after birth when there is an essential development of neural networks as an adaptive mechanism to the new environment (43, 47, 48). There is a shift towards more stable breathing patterns (lower respiratory rates and higher tidal volumes) and increasing ventilatory responses with postnatal age. Due to this maturation process, healthy young infants commonly have central apneas and periodic breathing during sleep, predominantly during REM sleep, that tend to resolve over the first 6 months of life with no need for breathing support (47). In addition, there is a progressive decrease in REM sleep over the first months of life with an increase in respiratory stability. Infants born preterm have more immature respiratory centers and weaker hypercapnic ventilatory response predisposing them to central apneas in the first weeks-months of life (47, 49). Exposure to hypoxia, hyperoxia and other non-respiratory stresses, such as exposure to chemicals or malnutrition, during the critical maturation period can permanently alter

respiratory control (48-50). Therefore, very young infants in need for breathing support during the first weeks/months of life may show changes in their breathing control and require close monitoring to avoid exposure that might impact the normal development of their breathing control mechanisms.

While a broad range of disorders affecting the CNS can impact breathing control, the majority of these impact the overall brain function, including breathing control, rather than specifically impairing central respiratory drive. *Acquired insults of the CNS* such as brain tumors, infections, trauma or infarctions can cause abnormalities in the central drive to breath and subsequent hypoventilation due to the injury itself or secondary to intracranial obstruction or brain stem compression (51). *Congenital central hypoventilation syndrome (CCHS)* is a rare disorder that causes hypoventilation due to a mutation in the paired-like homeobox 2B (PHOX2B) gene (52-55). While the mechanisms behind this primary hypoventilation are still being uncovered, it is hypothesized that there is a deficit in the integration of central chemoreceptor inputs causing an absence or extremely weak response to sustained hypercapnia, during all behavioral states (56). As a result, children with CCHS have a lifelong risk of central hypoventilation with a need for breathing support (57). Abnormalities of breathing control have also been described in other congenital conditions including *rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome, familial dysautonomia, mitochondrial encephalomyopathies, Rett syndrome, Prader-Willi syndrome, Arnold-Chiari malformation type II,* and *achondroplasia* (58-61). Children with these disorders may present with a broad range of respiratory impairment that may benefit from long-term NIV, either exclusively during sleep or more extended use.

1.3.2. Upper airway obstruction

Obstruction of the upper airway, from a small or collapsible airway, leads to an increased work of breathing and increase in the central drive to breath. The most common disorder of upper airway obstruction in children that leads to use of long-term NIV is obstructive sleep apnea (OSA). OSA is characterized by intermittent airway obstruction during sleep. This happens because of a combination of compromised airway anatomy and insufficient neuromotor response of the pharyngeal dilator muscles (62). Children with upper airway obstruction are able to maintain airway patency during wakefulness by augmented dilator muscle activation but these mechanisms are compromised during sleep leading to OSA (63); at sleep onset, skeletal muscle tone decreases and is further decreased during REM sleep. While anatomical airway compromise is an important factor contributing to OSA in children, it is not sufficient; not all children with a small or crowded airway will have OSA. Non-anatomical risk factors for OSA include a poor airway neuromotor response leading to airway collapse, a low arousal threshold leading to frequent awakenings from sleep, a high arousal threshold leading to maintained sleep in the face of respiratory gas disturbance, and high sensitivity of the ventilatory response system leading to respiratory instability. Therefore, there are different phenotypic causes for OSA that might respond different to therapies for OSA (64).

Upper airway obstruction leading to OSA has a range of causes in children that may benefit from long-term NIV. The most common anatomical factor leading to upper airway obstruction and increased risk of OSA in children is *adenotonsillar hypertrophy*. Adenotonsillectomy continues to be the first line treatment for OSA in children (65), with NIV as

an alternative therapy for those that are not surgical candidates or have residual OSA after surgery (66). Residual symptoms of OSA after adenotonsillectomy can be as high as 30%, being older ages (>7 years of age) and increasing BMI z-scores strong risk factors (67). Asthma and severe OSA pre-adenotonsillectomy are moderate risk factors in non-obese children. Other possible causes of upper airway obstruction include c*raniofacial abnormalities* such as isolated clefts, craniosynostosis, hypoplasia, hyperplasia, or multiple craniofacial anomalies in syndromic children such as Pierre Robin Sequence (68-70). *Airway malacia* is a common cause of functional upper airway collapsibility in early infancy that can lead to need for breathing support. *Premature* babies have more collapsible airway, predisposing them to obstructive and mixed apneas that may benefit from NIV support (47, 49). *Obesity* in children leads to airway compromise by causing a narrower airway caliber due to fatty infiltrates in peripheral tissues of the upper airway and shifts in blood volume from peripheral tissues to the neck (71). In addition, the presence of obesity may predispose to other respiratory physiologic mechanisms that contribute to impaired gas exchange such as falling lung volumes. Large epidemiological pediatric studies from countries around the world have shown that obesity is an independent risk factor for OSA and hypoventilation, with a recent study showing a rate of OSA as high as 44% (66, 72). Although adenotonsillectomy has been shown to be effective in children with OSA and obesity, up to 33% of obese children do not normalize polysomnographic findings after surgery and may require NIV for airway patency and normal gas exchange during sleep (65). Children with *cerebral palsy* are at higher risk for abnormal control of the upper airway muscle function resulting in greater collapse of the upper airway, where NIV has been shown to be beneficial (73, 74). Children with *NMD* are also at risk for OSA due to muscle weakness of their

pharyngeal dilator muscles leading to airway collapsibility during sleep (75, 76). In summary, there is a range of disorders with impairments contributing to upper airway obstruction and OSA where long-term NIV can provide benefit as a bridge to surgery or as an ongoing therapy.

1.3.3. Muscles weakness

A robust respiratory muscle response is necessary to maintain lung volume and blood gases levels including both oxygen and carbon dioxide. Children with significant muscle weakness may have difficulties generating normal tidal volumes despite recruitment of accessory respiratory muscles. Initial compensation for low volumes through an increase in respiratory rate can maintain normal gas exchange while awake (77). However, this compensating mechanism may be insufficient during sleep, particularly during the drop in muscle tone occurring in REM sleep. As muscle weakness escalates or demands on the respiratory system increase, compensatory mechanisms fail, areas of the lung become atelectatic with ensuing hypoxemia, progression to respiratory insufficiency, and ultimately respiratory failure. The respiratory decompensation may initially be limited to sleep but eventually leads to daytime chronic respiratory failure, which carries a poor prognosis; correction of nocturnal hypercapnia with NIV have been shown to reverse daytime hypercapnia (78, 79).

Other respiratory complications associated with muscles weakness can coexist and contribute to respiratory failure and need for NIV. These include: 1) impairment of airway clearance due to weak cough and retention of secretions resulting in microatelectasis; 2)

scoliosis, which is associated to reduction in chest compliance and restrictive lung disease; 3) swallowing dysfunction, poor airway protection and ultimately aspiration-related lung disease (76, 80).

There is a range of muscular dystrophies, congenital myopathies and musculoskeletal abnormalities potentially leading to respiratory insufficiency. Although prevalence, age of onset, severity and disease progression vary among these conditions, respiratory complications are the primary cause of morbidity and death for all of them and NIV is almost always required at some point in the lives of these patients (76). One example of NMD with early onset of respiratory complications and failure is *spinal muscular atrophy* (SMA), particularly SMA type 1 (SMA1) (76). Infants with SMA1 have significant muscle weakness and bulbar impairment leading to respiratory failure, profound airway clearance impairment, swallowing dysfunction and death before 2 years of age without breathing support (81-85). Children with SMA type 2 and 3 usually develop respiratory failure later in life and have longer rates of survival (86). *Duchenne muscular dystrophy (DMD)*, an x-linked defect in the dystrophin gene, is a NMD with progressive proximal muscle deterioration and loss of independent ambulation. Progression of muscle weakness and development of respiratory complications during the second decade of life results in nocturnal hypoventilation and ultimately chronic respiratory failure (87-90). The natural history of DMD has changed significantly since the introduction of corticosteroids as standard of care due to improvement in cardiorespiratory function and delayed need for NIV (91, 92). Elective use of NIV, techniques for cough augmentation, and cardio protective medications have also contributed to an increased life expectancy and likely health-related quality of life for children and young adults with DMD, although data on quality of life is scarce

(93). The American Thoracic Society (ATS) official statement for the respiratory care of patients with DMD published in 2004 recommends the use of nocturnal nasal NIV to treat sleep-related upper airway obstruction and chronic respiratory insufficiency in patients with DMD, and mouth-piece NIV for patients with daytime hypoventilation (94). Many other NMDs lead to the development of respiratory insufficiency with progression of muscle weakness, including all *congenital myopathies* and *muscular dystrophies*, and *severe kyphoscoliosis.* Acquired causes for severe myopathy such as *cervical spinal injury* can cause significant muscle weakness that, although not progressive, may result in respiratory insufficiency.

1.3.4. Impairments in gas exchange

Children with advanced lung diseases will have impaired gas exchange due to ventilation-perfusion mismatching with non-ventilated but well-perfused alveoli. Causes for this mismatching include severe air trapping (95), significant atelectasis/lung collapse (96), abnormal alveolar membranes (97), and severe arterial pulmonary vasoconstriction resulting in pulmonary edema (98). Regardless of the etiology, children with advanced lung impairment develop shallow breathing and tachypnea as a compensatory mechanism to reduce inspiratory muscle load and might progress into a status of high calorie burning, muscle fatigue and ultimately deterioration of gas exchange with hypoxemia and/or hypoventilation (40). NIV might be beneficial to unload respiratory muscles, increase alveolar ventilation and ultimately improve gas exchange.

Indication for NIV in children with chronic lung diseases and respiratory failure may include cystic fibrosis, bronchopulmonary dysplasia, interstitial lung diseases and any other

chronic lung disease. However, the evidence to support the use of NIV in these children is scarce. A recently updated Cochrane review found three trials that evaluated the use of nocturnal NIV in 27 children and adults with *cystic fibrosis* (99). The reviewers concluded that NIV in addition to oxygen may improve gas exchange during sleep to a greater extent than oxygen alone and improve exercise performance in moderate to severe disease. Other studies have described NIV use in individuals with cystic fibrosis although with very little evidence of benefit to support this use (100-102). While NIV has been used for over 40 years in premature infants with respiratory distress (103), studies assessing the use of long-term NIV in children with established *bronchopulmonary dysplasia* and impaired ventilation are lacking (104). The use of long-term NIV in children with other chronic lung diseases such as *bronchiolitis obliterans* and *interstitial lung diseases* has also not been studied.

There is a growing interest in the use of NIV in children with *heart failure* and associated central sleep apnea due to changes in chemoreceptor response secondary to delayed cerebral blood flow (105). However, the use of NIV to treat central sleep apnea in adults with heart failure have had controversial results, with failure to demonstrate improved survival despite improved oxygenation and cardiac ejection fraction (106, 107). To date, there have been no published studies assessing the use of NIV in children with cardiac conditions (104).

1.3.5. Multiple pathophysiological mechanisms leading to indication for non-invasive ventilation

It is common that children with complex medical conditions and syndromes have respiratory compromise with more than one cause. For instance, children with severe cerebral

palsy and other severe CNS disorders may have a combination of abnormalities in the central drive to breath, impaired pharyngeal muscle function resulting in OSA and chronic lung disease secondary to poor secretion management and chest compliance, all of them contributing to mixed sleep apnea (108). Children with Trisomy 21, for instance, may have a combination of anatomical factors such as airway narrowing, infiltrates of neck tissues, susceptibility to obesity and abnormal pharyngeal muscle function that increase the risk for OSA (60, 109-112), with potential benefits from NIV. Children with NMD may develop both muscle weakness of pharyngeal dilators leading to OSA and progressive weakness of respiratory muscles resulting in respiratory failure (76).

1.4. USE OF NON-INVASIVE VENTILATION TECHNOLOGY IN CHILDREN

The selection of the NIV technology is influenced by multiple factors, including the pathophysiology of the underlying condition and dependence on breathing support for each child as well as the devices and interfaces currently available in the market, which might vary through different ages. A good knowledge of the options available and its suitability for each child is important for choosing the right technology for an individual child.

1.4.1. Non-invasive ventilation devices

NIV technology has changed significantly since the development of the first CPAP devices. They are now smaller, lighter, quieter, portable and more sensitive to the patient's breathing (113). There are two main modalities of positive pressure ventilation used for NIV:

Continuous positive pressure (CPAP) applies a single pressure continuously throughout the entire breathing cycle. CPAP stents the airway and contributes to lung recruitment, relying on spontaneous breathing to allow normal oxygenation and CO_2 elimination. CPAP is the preferred therapy mode in children with upper airway obstruction and intact drive to breath. It may also be useful in children with increased respiratory load to help augment lung tidal volume and support lung recruitment, for instance, in children with bronchopulmonary dysplasia or diaphragm paralysis; this can improve oxygenation as well have a modest effect on CO_2 clearance.

Bi-level positive pressure (BPAP) consists of two pressure levels – a higher inspiratory positive airway pressure (IPAP) delivered during inspiration, and a lower expiratory positive airway pressure (EPAP) delivered at the end of expiration. This mode allows for augmentation of tidal volume during inspiration and maintenance of lung recruitment during expiration in patients with respiratory insufficiency due to impaired lungs. In addition, a back-up rate can be set to deliver breaths in the absence of a patient-initiated breath or insufficient respiratory muscle effort to trigger the machine. Further, BPAP can also be used for only purpose of airway patency when CPAP pressure is high enough to impede exhalation.

BPAP devices can be set in different ventilator modes (table 1.1), similar to those used for tracheal ventilation:

In s*pontaneous mode*, the ventilator detects changes in patients' inspiratory and expiratory flows to provide the adequate pressure with no limits in timing of components of the respiratory cycle. This mode can be used in children with a strong drive to breathe and allows maximum control of when breaths are initiated.

Spontaneous/timed mode is a common modality where a respiratory rate is set so to maintain a minimum breathing frequency. This can compensate for impairments in respiratory drive or when the respiratory muscle strength is insufficient to generate sufficient flow to trigger machine support.

Other modes include: 1) *Pressure-controlled mode*, when maximum pressure and inspiratory time (Ti) both are set so the ventilator cycles into expiration after a fixed period of time rather than in response to changes in patient's respiratory flow; 2) *Volume-preset ventilation*, when the ventilator delivers a fixed tidal volume in a set Ti with each breath, with no limits in the pressures required.

Intelligent modes have been developed in new devices with the aim of adapting the device to the patient's respiratory effort rather than the patient having to adapt to the device, such as auto CPAP and BPAP, and guaranteed tidal volumes such as average volume-assured pressure support (AVAPS) and adaptive servo ventilation (114, 115). Despite the efforts to develop more physiological modes of ventilation, studies have not demonstrated better efficacy or adherence with these new modalities (107, 116). Importantly, most of the NIV devices have been developed for adults, with manufacturer's specifications for minimum patient weight most typically starting at 10 to 30 kilograms, and, therefore, may not function properly in smaller patients.

Regardless of the selected NIV type and mode, it is imperative that prescribers understand the patient's underlying pathophysiology in order to set the mode and settings that better support the patient's respiratory cycle, keeping airway patency, allowing for

spontaneous breathing as much as possible and compensating for partial or total absence of patient's effort if necessary.

1.4.2. Non-invasive ventilation interfaces

There are different interfaces available for NIV including nasal masks, oro-nasal masks, full-face masks, helmets, nasal pillows and mouthpieces (117). Except for the mouthpiece and the helmet, current masks usually consist of a frame and a cushion that seals around the patient's nose or face, held in place with a headgear. Masks for home NIV devices with a single limb include an expiratory valve for exhalation, avoiding CO_2 accumulation. More recently, new masks specifically designed for children and multiple size options facilitate NIV use from infancy through adolescence. There is a growing interest in interventions to better choose masks and headgears for an optimal mask fit, more comfort, and less skin injury and other interface-related complications (118, 119). Early studies suggest that 3-dimensional (3D) scanning and printing technology may be used to customize masks in children with craniofacial abnormalities when the use of standard masks may be challenging (118, 120).

1.4.3. Additional technology related to non-invasive ventilation

Current NIV devices have heating and humidification systems that generate heated moisture with the pressurized air. New heated tubing systems also contribute to the maintenance of air temperature and optimal humidity. These systems are meant to mimic the nose function and reduce airway resistance. Although large studies comparing humidified

versus non-humidified devices are not available, the use of heated humidification has been shown to decrease airway resistance, reduce leak and improve comfort and, therefore, has become standard of care (121, 122).

1.4.4. Nocturnal versus day and night use of non-invasive ventilation

NIV is predominantly used as an intermittent therapy, most commonly during nocturnal sleep. There are no objective studies assessing the number of NIV hours required to provide optimal benefit in children across ages. Some children may also benefit from NIV use during daytime naps, particularly infants who have long periods of sleep during the day (123). Children with advanced respiratory failure might require extended hours of NIV use during wakefulness to reduce respiratory symptoms, unload respiratory muscles and maintain normal gas exchange. In contrast, limits in terms of the maximum number of NIV hours have not been well described in pediatric populations and often remain controversial. Near 24-hour NIV support is generally used as a short-term treatment, for instance during an acute exacerbation, palliative care, or as bridge for more definitive treatments such as surgery or lung transplantation (102). Based on expert opinion, the British Thoracic Society guidelines for children with neuromuscular disorders recommends consideration for tracheal ventilation when there is NIV dependence for greater than 16 hours per day, or failure to correct abnormalities (76). The official ATS clinical policy statement for CCHS recommends deferring the use of NIV until 6 to 8 years of age in children requiring exclusively nocturnal NIV (124), although again this recommendation is based on expert opinion as no prior studies have compared NIV versus

tracheal ventilation in children with CCHS. A discussion with the child and family about goals of care and safety measures becomes important in case of prolonged NIV.

1.5. CONTRAINDICATIONS, ADHERENCE AND COMPLICATIONS RELATED TO LON-TERM NON-INVASIVE VENTILATION

The benefits of NIV can be limited by a number of factors. Although most of the contraindications are relative, a few absolute contraindications need to be considered during the initial assessment. As with any other long-term therapy, adherence is key and sometimes challenging with multiple factors involved in relation to the child, technology and the social/family environment. Further, there are potential short and long-term side effects from NIV, some of them specific to pediatrics that required careful monitoring.

1.5.1. Contraindications for non-invasive ventilation

There are limited absolute contraindications for NIV. Severe bulbar dysfunction, inability to manage secretions, and a low level of consciousness are the major contraindications for NIV due to the high risk for aspiration. Children with severe central hypoventilation, critical airways, and advance respiratory failure leading to diurnal hypoventilation might not be ideal candidates for long-term NIV (54, 76).

1.5.2. Adherence to long-term non-invasive ventilation therapies

One important challenge in the use of NIV is tolerance and adherence, both at initiation and over time. NIV devices now provide objective measurements of NIV use, allowing

monitoring of adherence. Prior studies on adherence to long-term NIV in children have used different objective and subjective measures with a range of definitions for acceptable adherence. One retrospective study published in 2006 showed daily CPAP use in 75% of children at 46 months but mean daily use was only 4.7 hours (125). Other studies including prospective observational studies and multicenter randomized trials have found low adherence rates despite high efficacy of the therapy, with mean nightly use below 6 hours (114, 115, 126, 127).

Multiple factors may influence adherence to NIV in children. Several studies identified a variety of risk factors for poor adherence including older children and adolescents, males, children with developmental delay, children with anxiety and depression, and a lack of perceived benefit from NIV (126, 128-131). In contrast, other studies did not support these findings (127, 128, 130, 132-135). A questionnaire-based study prior to CPAP initiation found that the greatest predictor of NIV use was maternal education, with an inverse correlation with age and African-American race (126). A qualitative study of adolescents using CPAP highlighted several barriers for adherence including home structure, social reactions to CPAP, communication between family members, and perception of benefit (131).

Equipment can also impact NIV adherence. While oro-nasal mask type has widely been reported to cause poorer adherence in adults (136), only one pediatric study has found this association (132). Difference in adherence by NIV mode were studied in a randomized double-blind trial where children with OSA were assigned to CPAP or BPAP. Even though both modes were highly effective, the dropout rate was high and NIV use was suboptimal in both groups,

with no differences between NIV modes (115). A later randomized clinical trial showed similar results (114).

Multiple studies have attempted to demonstrate strategies that facilitate NIV initiation and long-term compliance. The combination of multi-disciplinary team approach, behavioral modification strategies or use of remote systems and smartphone applications to monitor NIV adherence have all been shown to impact NIV adherence (55, 129, 137-141). Most of these studies, however, lacked a control group. Efforts to optimize mask fit, adequate settings for the child's underlying pathophysiology, use of heating and humidification systems, longer tube systems allowing the child to move without disconnection from the device, and close monitoring of these children all seem to be reasonable strategies to consider when initiating NIV, but there is no clear evidence available to demonstrate which ones may result in better long-term compliance (130, 132, 135).

1.5.3. Complications from long-term non-invasive ventilation

Skin breakdown is a common complication derived from the application of pressure from the mask interface that reduces blood flow under the contact area resulting in injury. Skin injuries can range from transient erythema to deep ulcers that can compromise the use of NIV (142). In addition, friction and increased temperature and humidity inside the mask can also contribute to skin injury, particularly in the nasal bridge (143, 144). Preterm infants, children under 2 years of age, children with craniofacial abnormalities, and use of oro-nasal mask confer higher risk for skin injury (119, 143). A pediatric study using 3D surface imaging of the face and measurements of skin hydration determined skin changes in up to 82% of their subjects (119).

Appropriate mask fit, avoidance of excessive tightening, good mask hygiene and adequate mask replacement could significantly reduce skin complications (118, 120, 142).

Midface hypoplasia and skull bone indentation have also been described in the literature, resulting from prolonged application of pressure over growing facial bones. A recent study using serial cephalographic images to determine mean annual change in midface structures in children pre and post-long-term NIV demonstrated retrusion of the midface, rotation of palatal plane, and upper incisor flaring in compliant children compared to the forward growth seen in noncompliant subjects (145). The cause-effect relationship and possible risk factors are not clear. One study found that only the number of NIV hours correlated with the presence of midface hypoplasia, with no significant association between midface hypoplasia and age, underlying disease or mask type (142).

Other commonly reported side effects include eye irritation, discomfort, nasal dryness and congestion, mouth leak, and abdominal distension. The potential risk for pneumothorax and tympanic rupture due to excessive pressures in closed cavities has also been reported in a few case reports (118).

1.6 SUMMARY

The increased use of long-term NIV to treat sleep and breathing disorders in children has likely been driven by advancements in medicine and NIV technology, along with greater recognition by clinicians for NIV as a feasible option in the provision of long-term respiratory support in a home-based setting. Little work has been undertaken to systematically summarize the existing knowledge on this important field. Limited information is available regarding recent

changes in the population of children receiving long-term NIV. Despite this increased use of long-term NIV in children, there is a paucity of longitudinal data on long-term outcomes.

1.7 AIMS AND HYPOTHESIS

1.7.1. Aims

The overarching aim of this thesis is to understand the factors that impact the use and outcomes of long-term NIV in children with the goal of improving how we care for this group of children.

The specific aims of this thesis are:

1. To summarize the available data on the use of long-term NIV in children, identify data appropriate for systematic review, and identify gaps in current knowledge.
2. To describe longitudinal trends in the clinical characteristics, NIV technology use and long-term outcomes of children receiving long-term NIV over a 10-year period.
3. To describe longitudinal changes in sleep, breathing and growth, as well as adherence and complication rates for children receiving long-term NIV.

1.7.2. Hypothesis

1. Despite a large body of literature describing the use of long-term NIV in children, there are significant gaps in knowledge related to the indications, benefits and other important outcomes such as adherence and side effects.
2. As NIV use has become more common, there has been a greater diversity, higher complexity, and increased severity of sleep-related breathing disorder in children receiving long-term NIV.

3. Efficacy and benefits in sleep, breathing and benefits and growth derived from long-term NIV therapy are sustained over time, while adherence improves, and complications resolve.
4. Survival rates have remained high over time, with no changes in mortality rates.

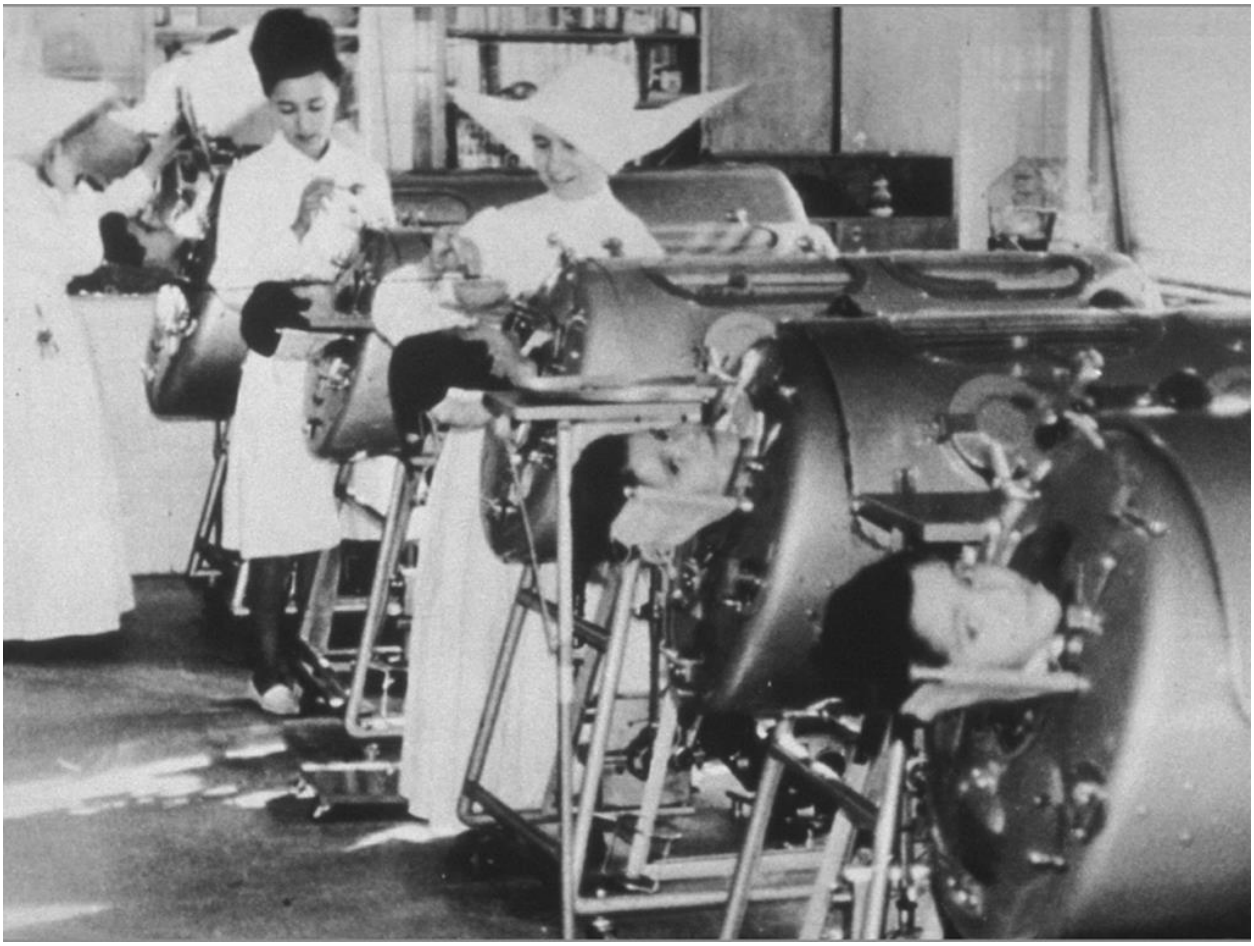

Figure 1.1. Children on iron lung therapy at the Nino Jesus university Hospital in the early 1920s. With permission from the hospital's archives.

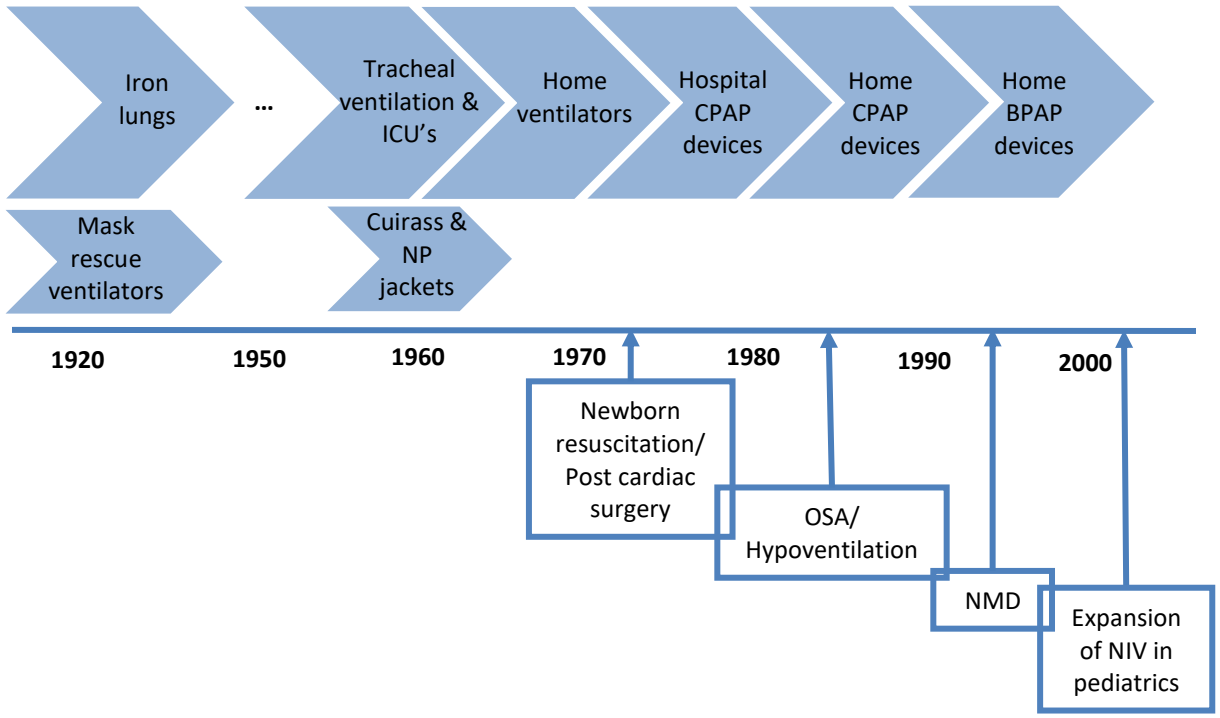

Figure 1.2. Historical perspective of the use of mechanical ventilation in pediatrics. BPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; ICU, intensive care unit; NP, negative pressure.

Table 1.1. Bilevel positive airway pressure (BPAP) modalities.

MODES	CHARACTERISTICS	ADVANTAGES	DISADVANTAGES	INDICATIONS
PRESSURE PRESET				
Spontaneous	- Adjust pressures based on patient's spontaneous breathing - Unlimited Ti	- Better synchronization - Compensate leaks	- Does not provide support in patients unable to trigger machine (i.e. central apneas, muscle weakness)	- Respiratory conditions - UA obstruction requiring high CPAP pressures
Spontaneous/timed	- Adjust pressures based on patient's spontaneous breathing - Back-up timed respiratory rate	- Allows spontaneous breathing - Machine provides a breath if respiratory rate falls below a set rate - Compensate leaks	- Asynchrony in high set rates - CO_2 retention due to short expiratory times is possible in high set rates	- Abnormal breathing control - Difficulties triggering machine (i.e. muscle weakness)
Controlled	- Preset maximum pressure - Preset Ti	- Compensate leaks	- Asynchrony - Risk for CO_2 retention	-
VOLUME PRESET	- Fixed tidal volume - Fixed Ti	- Stable volumes - No trigger needed	- No maximum pressure set - Asynchrony - Does not compensate leaks	- Daytime ventilation through a mouth piece

CPAP, continuous positive airway pressure; Ti, inspiratory time; UA, upper airway.

CHAPTER 2: LONG-TERM NON-INVASIVE VENTILATION THERAPIES IN CHILDREN: A SCOPING REVIEW PROTOCOL

2.1. INTRODUCTION

Ideally, stakeholders in health care use research evidence to inform their decision-making. When the topic of interest is broad, it may be challenging to locate information, organize and summarize it in a format that is meaningful and relevant. For this task, a scoping study is a type of systematic review that aims to map relevant literature in the field of interest with the aim of highlighting the key concepts and identifying the main sources and types of evidence.

For this thesis, we developed a full methodology including a qualitative approach for identification of areas of interest, refinement of the research question, agreement on terms to be included in the search strategy, and identification of sources of grey literature through the establishment of a committee of experts in the field of pediatric and respiratory medicine and methodologists with large experience in systematic reviews. Several rounds of expert consultation resulted in the development of a protocol in sufficient detail to enable reproducibility, which is presented in chapter 2 and published in a relevant journal. A final manuscript, presented in chapter 3, was published in a high impact journal and results were disseminated in multiple national and international forums.

Article published as: Castro Codesal ML, Featherstone R, Martinez Carrasco C, Katz SL, Chan EY, Bendiak GN, Almeida FR, Young R, Olmstead D, Waters KA, Sullivan C, Woolf V, Hartling L, MacLean JE. Long-term noninvasive ventilation therapies in children: a scoping

review protocol. BMJ Open 2015; 5: 8 e008697. DOI: 10.1136/bmjopen-2015-008697.

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2.2. ARTICLE 1: LONG-TERM NON-INVASIVE VENTILATION THERAPIES IN CHILDREN: A SCOPING REVIEW PROTOCOL

2.2.1. Abstract

Introduction: Non-invasive ventilation (NIV) in children has become an increasingly common modality of breathing support where pressure support is delivered through a mask interface or less commonly through other non-invasive interfaces. At this time, NIV is considered a first line option for ventilatory support of chronic respiratory insufficiency associated with a range of respiratory and sleep disorders. Previous reviews on the effectiveness, complications and adherence to NIV treatment have lacked systematic methods. The purpose of this scoping review is to provide an overview of the evidence for the use of long-term NIV in children.

Methods and analysis: We will use previously established scoping methodology. Ten electronic databases will be searched to identify studies in children using non-invasive ventilation for longer than 3 months outside an intensive care setting. Gray literature search will include conference proceedings, thesis and dissertations, unpublished trials, reports from regulatory agencies and manufacturers. Two reviewers will independently screen titles and abstracts for inclusion, followed by full text screening of potentially relevant articles to determine final inclusion. Data synthesis will be performed at three levels: 1) an analysis of the number, publication type, publication year, and country of publication of the studies; 2) a summary of the study designs, and outcomes measures used; 3) a thematic analysis of included studies by subgroups. **Ethics and dissemination**: This study will provide a wide and rigorous overview of the evidence on the use of long-term non-invasive ventilation in children and provide critical information for health care professionals and policy makers to better care for this group of

children. We will disseminate our findings through conference proceedings and publications and evaluate the results for further systematic reviews and meta-analysis.

2.2.2. Background

The purpose of this scoping review is to provide a rigorous overview of the evidence for the use of long-term NIV in children with respiratory and/or sleep disorders. NIV in children is an increasingly common modality of breathing support where a mask interface, rather than an endotracheal tube or tracheostomy, is used to connect to pressure support. Long-term use of NIV provides an option for children who require intermittent ventilatory support (i.e. for sleep only) or as part of palliative care. The use of NIV in children has expanded worldwide including developing countries, since its first reported use in the early 1990s, resulting in a decrease in the use of long-term invasive ventilation via tracheostomy (14, 17-19, 21, 24, 26, 27, 146-148). Factors contributing to the increased use of NIV likely include increased survival of children with complex medical conditions, a shift in the emphasis of health care from hospital to home based care, and technological advances in the masks and machines to support home use of NIV in children.

Today, NIV is considered a first line option of ventilatory support for chronic respiratory insufficiency associated with a range of respiratory and sleep disorders including chronic respiratory failure (149-151), cystic fibrosis (95, 152-154), musculoskeletal weakness or chest wall restriction (83, 87, 155-158), obstructive sleep apnea (OSA) and craniofacial malformations (61, 159-161), sleep disorders associated with neurological conditions and abnormalities in central respiratory drive (54, 162-164). Long-term NIV has been used successfully in infants, from the first weeks of life. It has been shown NIV can be used long-term across all age groups (38, 165-168). Safety and efficacy of NIV use in children have been documented for children with certain underlying conditions such as neuromuscular disease or OSA (80, 169, 170).

Adherence to NIV therapy is also an outcome of interest as there are considerable challenges in establishing and maintaining use of NIV in children (114, 115, 125, 131, 132, 137). Reported benefits of NIV use in children are broad and include outcomes related to acute illness (171), chronic respiratory function (154, 157, 172), sleep and daytime function (161, 173, 174), behaviour and neurocognitive outcomes (175), general health outcomes (156), quality of life (173, 176), progression of underlying disease, and survival (176, 177). Funding for NIV and access to this technology are also important considerations (178).

Previous reviews on long-term NIV use in children have lacked systematic methodology or NIV in children has been included in systematic reviews of broader topics. From a preliminary search strategy using terms related to NIV and children, we identified 758 review articles of which 91 may have some information relevant to long-term NIV use in children. Of these, only eight previous reviews described a search strategy or systematic methodology (179-181). Of note, none of the reviews had a specific focus of enquiry regarding long-term use of NIV in children but rather included NIV as one possible intervention for a particular pediatric population. Moreover, only four of these reviews had a specific section on NIV or included studies with NIV interventions. The aim of this scoping review is to define the body of literature relevant for the use of long-term NIV in children and provide a systematic overview of the existing evidence. Using this process, we will not only define the scope of existing data but also determine if there is sufficient literature relevant to subgroups that would be appropriate to apply systematic review or meta-analysis methodology.

2.2.3. Methods and analysis

Study design: The methodology of this scoping review is based on the methodological frameworks developed by Bragge *et al*. and Arksey and O'Malley (182, 183). The results will be reported following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols 2015 statement" (184). This approach will enable a rational assessment of the evidence that is available on long-term NIV interventions in children and ensure a transparent and complete report of the same.

We gathered an advisory team of experts in systematic reviews, pediatric respirologists, sleep medicine specialists, pediatric nurse practitioners and industry representatives, to provide input on the search strategy as well as in the discussion of the results of the scoping review. In addition, children using long-term NIV and their caregivers have been included in the advisory team with the aim of prioritising the outcomes identified in this scoping review from the patient and caregiver perspective as well as identifying important outcomes that have not been included in previous studies.

Eligibility criteria:

Types of Participants/ Population: Studies reporting results for children from newborn to age 18 years will be included. Studies that include both adults and children will be included if data for children is reported separately.

Types of Interventions: Eligible studies must contain information on NIV use defined as the administration of breathing support delivered through a non-invasive interface most commonly a nasal or face mask but also a mouth piece or abdominal belt. Types of breathing support includes (1) positive pressure support including continuous positive airway pressure (CPAP) or

an inspiratory and expiratory airway pressure (bi-level), (2) negative pressure ventilation (NPV). Similar to the definition we found in other review articles from the preliminary search review, we will define long-term use as the use of NIV for at least 3 months outside an acute care environment. This may include, but not be limited to, use of NIV in community-based settings such as homes, a family or group home, or specialized non-acute hospital-based units. This definition is intended to include children with chronic conditions that require long-term NIV and are stable enough to receive ventilatory therapy at home or in a chronic care environment. Articles that describe long-term use of NIV with no time specification will be included if there is a clear intention of treating a chronic problem.

Type of outcomes: No restriction with regards to outcomes will be applied.

Types of Studies: Original studies published from 1990 onwards will be considered for inclusion including randomized and non-randomized clinical trials, controlled before- after, cross-sectional studies, longitudinal observational studies, retrospective cohorts, qualitative and mixed methods research and case series with three or more cases; 1990 was determined as a starting date because the first study of long-term NIV use in children we identified was published in 1992.

Exclusion: Case reports, case series with less than three subjects, comments, editorials, letters and reviews will be excluded. Studies where NIV is used solely for the treatment of acute illness will be excluded. During the full text screening, only articles in English, French, Spanish, Portuguese, Italian and Catalan will be included as the review authors are proficient in those languages.

Information sources: An information specialist working for the Alberta Research Centre for Health Evidence (ARCHE) at the University of Alberta collaborated with investigators to design a comprehensive and sensitive search strategy with terms for non-invasive ventilation and children from newborn to age 18 years. The search strategy (Table 2.1) was developed for Ovid Medline with a validated child search filter (185), and will be translated into Ovid Embase, PubMed (last year only), CINAHL via EbscoHOST, and Wiley Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database). Database search results will be limited to human studies published after 1990. No language or study design restrictions will be applied.

Reference lists of all studies selected for this scoping review will be scanned to identify further relevant studies not detected by the search strategy.

We will also search for gray literature (non-peer reviewed investigations) including conference proceedings, thesis and dissertations, unpublished trials, regulatory agencies and manufacturers reports. In consultation with the advisory team, a list of conference proceedings and annual meeting reports to review from January 2012 to December 2014 will be established. The information specialist will search websites of the conferences relevant to NIV such as the American Thoracic Society, the American College of Chest Physicians, the Canadian Thoracic Society, the European Respiratory Society, the American Academy of Sleep Medicine, the European Society of Sleep Research, the Australasian Sleep Association, and the American Association of Neuromuscular and Electrodiagnostic Medicine. Investigators will search for publications of relevant proceeding abstracts or contact presenters to request study data if

needed. ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform will also be searched for trials registered after 2012 on NIV and positive airway pressure. Investigators will search for publications of relevant trials or attempt to contact study coordinators to request unpublished data. Regulatory agencies will be searched for ventilator device approval documents, premarket notifications, recall notices and safety advisories. Government sources will include Health Canada's Medical Device Active License Listing (MDALL), the U.S. Food and Drug Administration (FDA) device website (Devices@FDA), the Australian Government's Department of Health and Ageing Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications, the European Medicines Agencies, and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe: Medical Devices). Device manufacturers may be contacted with requests for premarket trial data. ProQuest Theses & Dissertations will also be searched for theses submitted after 1990 on non-invasive ventilation in children.

The Ovid Medline search strategy and the list of information sources will be approved by the advisory team prior to running the searches.

Study records

Data management: Results of searches will be imported into an EndNote library, and duplicates will be removed. Two exact copies of the EndNote library will be created for independent screening by two reviewers.

Selection process: Two independent reviewers will screen titles and abstracts of retrieved articles for eligibility based on the inclusion criteria. The full text will be retrieved for all potentially relevant articles; each will be evaluated independently for eligibility by two

reviewers. Discrepancies will be resolved through discussion between the reviewers to establish the final list of studies to be included in the scoping review. Reasons for exclusion will be recorded at the full text review.

Data collection process: Data extraction will be completed by one reviewer using a pre-designed standardized form and entered into Microsoft Excel database (Microsoft, Redmond, Washington, USA). Data extraction will be verified by a second reviewer for a sample of 10% of the studies. The data extraction form is based on Bragge *et al*. data extraction database and modified for this project to ensure that appropriate and relevant data is obtained (Table 2.2). [56] When there is missing information, two attempts to contact the corresponding authors will be made to obtain additional data. To avoid double counting in the instance of the same data set published in more than one publication, only one article per data set will be retained.

Data synthesis: The identified evidence will be collated using a specific analytical framework in order to present a narrative account of the existing literature.

Once the information has been extracted, we will present a narrative account of findings in three different ways: 1) a basic numerical analysis of the number, publication type, publication year, and country of publication of the studies included in the review. 2) A narrative description of the study design, aims, participant characteristics, sample size, intervention type, control group description, outcomes measures, and statistical methods. We will use this information to establish subcategories of studies which may include grouping based on age (e.g. infants, children, and adolescents), intervention type (e.g. CPAP, bi-level, and NPV) and disease categories (e.g. OSA, neuromuscular disease). 3) A thematic analysis of included studies

by subgroups if appropriate. The results will be presented based on the priorities established by our advisory team including input from children using NIV and their caregivers.

Timeline: We anticipate finishing the search, screening, data extraction and synthesis within 6 months. A search update may be required if the timeline is longer than expected.

2.2.4. Conclusion

This scoping review will be the first, to our knowledge, to provide a systematic overview of the evidence on the use of long-term NIV in children. The findings from this review will provide stakeholders with a rigorous research base to support health care providers to improve clinical practice and policy makers to support resource needs for this complex group of children. We will disseminate our findings through conference proceedings and publications. The gathered data can be used to inform the development of guidelines for the care of children using long-term NIV and will identify gaps in knowledge to support future research endeavors. Based on the results, we will determine whether the application of other systematic review methodologies, such as meta-analysis or meta-synthesis, will be appropriate for any of the subgroups that we identify for future research.

Table 2.1. Search strategy developed for MEDLINE using OVID

Search terms
1. Continuous Positive Airway Pressure/
2. Noninvasive Ventilation/
3. Intermittent Positive-Pressure Breathing/
4. Ventilators, Negative-Pressure/
5. AVAPS.tw.
6. ((auto* or adaptive) adj2 (servoventilation or ventilation)).tw.
7. AutoSet*.tw.
8. ((bi level or bilevel) adj2 (airway* or air way* or assist* or breath* or positive pressure* or respirat* or ventilat* or support* or therap*)).tw.
9. BIPAP*.tw.
10. BPAP*.tw.
11. c flex.tw.
12. CNEP.tw.
13. (continuous negative adj2 pressure).tw.
14. (continuous positive airway* or continuous positive air way*).tw.
15. (continuous positive adj2 pressure).tw.
16. CPAP*.tw.
17. ((domicil* or home*) adj5 ventilat*).tw.
18. intermittent positive pressure breathing.tw.

19. IPPB*.tw.

20. ((long term or longterm) adj5 ventilat*).tw.

21. ((nasal* or mask*) adj2 (positive adj2 pressure)).tw.

22. ((nasal* or mask*) adj2 ventilat*).tw.

23. nCPAP*.tw.

24. ((negative pressure) adj2 (respirat* or ventilat*)).tw.

25. ((night* or nocturnal* or sleep*) adj5 ventilat*).tw.

26. NIPPV*.tw.

27. ((noninvasive adj5 ventilat*) or (non invasive adj5 ventilat*)).tw.

28. (noninvasive respiratory support* or non invasive respiratory support*).tw.

29. NPPV*.tw.

30. (positive pressure adj2 respirat*).tw.

31. REMstar*.tw.

32. (tank adj (respirat* or ventilat*)).tw.

33. VPAP*.tw.

34. or/1-33

35. Hypoventilation/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]

36. Interactive Ventilatory Support/

37. Intermittent Positive-Pressure Ventilation/

38. Positive-Pressure Respiration/

39. Respiration, Artificial/

40. Respiratory Insufficiency/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]

41. exp Sleep Apnea Syndromes/ pc, rh, th [Prevention & Control, Rehabilitation, Therapy]

42. Ventilators, Mechanical/

43. ((airway* or air way* or breath* or inspirat* or respirat* or ventilat*) and (positive adj2 pressure)).tw.

44. intermittent positive pressure.tw.

45. IPPV*.tw.

46. (mechanical adj (respirat* or ventilat*)).tw.

47. (positive adj2 pressure adj (assist* or support* or therap*)).tw.

48. positive airway pressure.tw.

49. pulmonary ventilator*.tw.

50. respiratory support*.tw.

51. or/35-50

52. (noninvasive or non invasive or spontaneous*).mp.

53. 51 and 52

54. 34 or 53

55. exp Adolescent/

56. exp Child/

57. exp Infant/

58. exp Minors/

59. exp Pediatrics/

60. exp Puberty/

61. exp Schools/

62. adoles*.mp.

63. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).mp.

64. (boy* or girl* or teen*).mp.

65. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).mp.

66. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).mp.

67. minors*.mp.

68. (paediatric* or peadiatric* or pediatric*).mp.

69. (prepubescen* or pubescen* or pubert*).mp.

70. or/55-69

71. 54 and 70

72. (case reports or comment or editorial or letter).pt.

73. 71 not 72

74. exp animals/ not humans.sh.

75. 73 not 74

76. limit 75 to yr="1990 -Current"

77. remove duplicates from 76

Table 2.2. Data extraction form

Study characteristics	Extracted data
General information	First author last name Title Journal Publication year Country of study/Continent/Multi-national Publication type: journal, abstract, dissertation, unpublished trial, report
Introduction	Aims of the study Study research question Study population: number of subjects using NIV, mean age, age range, gender, primary underlying condition, comorbidities
Design	Study design: - Quantitative: randomized controlled trial, non-randomized controlled trial, controlled before-after, observational, cross-sectional - Qualitative: case series, ethnography, grounded theory, phenomenology, other, mixed methods Sample size

	Intervention type, NIV term used, interface type, duration of intervention, co-interventions Statistical analysis methods used Control group: number of control subjects, y/n, intervention in control group
Outcomes measures (whether self-reported or objective tools) *	Primary outcomes Secondary outcomes Adverse outcomes Duration of the follow-up
Authors conclusions	Positive, negative, neutral, indeterminate
Gaps and limitations identified by authors	

* Units of measurements will be reported.

CHPATER 3: LONG-TERM NON-INVASIVE VENTILATION IN CHILDREN: RESULTS OF A SCOPING REVIEW

Article published as: Castro Codesal ML, Dehaan K, Featherstone R, Martinez Carrasco C, Katz SL, Chan EY, Bendiak GN, Almeida FA, Olmstead D, Young R, Woolf V, Waters KA, Sullivan C, Hartling L, MacLean JE. Long-term non-invasive ventilation therapies in children: a scoping review. Sleep Med Rev 2017; 37: 148-158. DOI: 10.1016/j.smrv.2017.02.005. Permission for data reproduction was obtained from the journal.

3.1. ARTICLE 2: LONG-TERM NON-INVASIVE VENTILATION THERAPIES IN CHILDREN: A SCOPING REVIEW

3.1.1. Summary

Long-term non-invasive ventilation (NIV) is a common modality of breathing support used for a range of sleep and respiratory disorders. The aim of this scoping review was to provide a summary of the literature relevant to long-term NIV use in children. We used systematic methodology to identify 11,581 studies with final inclusion of 289. We identified 76 terms referring to NIV; the most common term was NIV (22%). Study design characteristics were most often single center (84%), observational (63%), and retrospective (54%). NIV use was reported for 73 medical conditions with obstructive sleep apnea (OSA) and spinal muscular atrophy (SMA) as the most common conditions. Descriptive data, including NIV incidence (61%) and patient characteristics (51%), were most commonly reported. Outcomes from sleep studies were reported in 29% of studies followed by outcomes in 19%. Adverse events and adherence were reported in 20% and 26% of articles respectively. Authors reported positive conclusions for 73% of articles. Long-term use of NIV has been documented in a large variety of pediatric patient

groups with studies of lower methodological quality. While there are considerable data for the most common conditions, there are fewer data to support NIV use for many additional conditions.

3.1.2. Introduction

NIV, where assistance to breathing or full ventilation is delivered through an interface outside the airway, has become the first line therapy for a wide range of sleep and respiratory disorders in children including upper airway obstruction (66, 159, 186), musculoskeletal weakness and chest wall restriction (61, 158, 162, 187-189), chronic lung diseases (38, 102, 154), CNS disorders (54, 164, 190), and other systemic disorders with respiratory insufficiency (191-193). Technological advances in NIV have provided children requiring long-term respiratory support and their families an acceptable alternative to invasive mechanical ventilation (IMV) via tracheostomy (194). Additional contributors to the increase in long-term NIV use include increased survival of children with complex medical conditions (28), a shift in health care from hospital to home-based care (28), and increased awareness of the consequences of sleep breathing disorders and their possible treatments (36, 37). NIV use has increased worldwide (14, 15, 17-19, 21, 23, 24, 26, 27, 148, 165), resulting in a reduction in the number of admissions to pediatric intensive care units and a greater number of children living at home using NIV (166, 168, 195).

There are gaps in our present knowledge on the benefit of long-term NIV in children. For instance, the literature on decreased mortality and morbidity rates and improved longevity with long-term NIV has focused primarily on neuromuscular diseases (NMD) such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA), with limited data on the impact on survival in other populations (15, 81, 93). Other outcomes, such as improvement in quality of life, neurocognitive and behavioral outcomes have been demonstrated in children using NIV for the treatment of obstructive sleep apnea (OSA); however, these benefits may not generalize to

children with other conditions needing NIV (66, 115). Long-term NIV use has been reported for conditions including a range of syndromes (186, 192, 196-201), congenital heart defects (202), obesity (203), sickle cell disease (191), and cancer (193).

In addition to an expanding range of conditions where NIV may be beneficial, the increase in long-term NIV use at home, as opposed to in hospital, has resulted in a shift in the responsibility of care to parents and caregivers (192, 204). Long-term NIV presents challenges including the use of a mask interface (142, 169), adherence (114, 131, 132), and funding for equipment as well as access to support services in the community (178). With increasing use of this technology, it is important to define the evidence-base to support the use of long-term NIV therapy in children, identify evidence gaps, and develop a research strategy to begin to address these gaps in knowledge.

To date, there has been no review of long-term NIV use in children employing systematic methodology. While prior systematic reviews have included information on long-term NIV in children, the focus of these reviews has been on diagnosis or treatment for specific conditions such as OSA, achondroplasia, global developmental delay or chronic cough (66, 92, 110, 164, 179-181, 205-207). The aim of this scoping review is to provide an overview of the literature relevant to long-term NIV use in children. The results of this scoping review will provide a map of all existing literature and will define the volume and characteristics of the primary research pertinent to long-term NIV use in children. We will use this map to identify data appropriate for systematic review and to highlight gaps in knowledge relevant to improving the care of children using long-term NIV.

3.1.3. Materials and methods

The scoping review protocol was designed based on the frameworks developed by Bragge and colleagues and Arksey and O'Malley (182, 183) with full details of the protocol published elsewhere (208). Scoping reviews are used to examine the main sources and types of evidence available with a broad approach to a topic; this is in contrast to a systematic review which usually addresses a narrow research question. As a result, scoping reviews are used to identify the boundaries and context of a topic area as well as summarize the key characteristics and results of included studies rather than appraise the quality of the evidence or provide a synthesis of the data. We created an advisory committee of experts in systematic reviews, pediatric respiratory and sleep medicine, and NIV therapies, to advise on the search strategy as well as in the reporting of the results.

Search strategy: An information specialist developed the search strategy for Ovid Medline with terms related to NIV and a validated child search filter (185), and then translated this into Ovid Embase, PubMed (last year only), CINAHL via EbscoHOST, and Wiley Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database; see On-line supplement for search strategy). Searches were limited to human studies published after 1990 because the first study of long-term NIV use in children we identified was published in 1992. No language or study design restrictions were applied to the search. Database searches were run between November 17 and November 28, 2014. An update of the literature search was conducted in 5 databases

(Ovid Medline, Cochrane Library, Ovid Embase, CINAHL and PubMed) on April 29, 2016 using the same search strategy to identify recently published studies and abstracts. Gray literature sources were searched between January 7 and January 21, 2015. We searched peer-reviewed abstracts from 10 selected conferences on respiratory, sleep, and neuromuscular medicine conducted between January 2012 and December 2014. We also searched theses and dissertations from 1990 onward via ProQuest Dissertations & Theses Global, trial registries from 2012 to 2014 via ClinicalTrials.gov and WHO's International Clinical Trials Registry Platform, and regulatory agencies and manufacturer reports from 1990 onward.

Inclusion criteria: Child was defined as newborn to 18 y of age. Studies with both adults and children as subjects were included if data for children were reported separately. Studies which included children and young adults were included if the mean age of the subjects was 18 y or younger. We defined NIV as any mode of ventilatory support that was delivered with a non-invasive interface which avoids tracheal intubation. This included both positive pressure, such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP), and NPV (see on-line supplement for the 48 terms used to define NIV). Long-term use was defined as at least three months of use outside an acute care environment. Study selection was not limited by study design or outcomes assessed. Case reports with three or more subjects were included. Comments, editorials, letters and reviews were excluded.

Study selection: Two reviewers screened English titles and abstracts of retrieved studies for eligibility. The same two reviewers screened full-text studies for the final list of included studies. Discrepancies were resolved by consensus. Studies written in English, Spanish, French, Portuguese, Italian and Catalan were included, with all other languages excluded.

Data extraction*:* Data extraction were completed using a pre-designed form and entered into a Microsoft Access Database (Microsoft, Redmond, Washington, USA). Extracted data included study design and duration, NIV terms used, medical conditions of studied populations, NIV intervention type and outcomes of interest identified in the methods' section of included articles. Data on NIV terms and medical conditions was exactly extracted as described by authors in the methods sections, with no interpretation of terms (e.g. if authors said OSA, we did not reword it into sleep disordered breathing). More than one term related to NIV or several medical conditions could be extracted from the same paper. Data about sample size, additional outcomes, adverse events, and adherence was extracted from the results sections. Outcomes were not defined a priori and were classified according to the data source (e.g. reported clinical information from medical letters, sleep study results, downloads from NIV machine, etc.). Comparisons where the statistical test had a $p<0.05$ were considered to show statistically significant differences. Data on author's conclusions and identified gaps in knowledge were gathered from the conclusion sections. Conclusions about NIV were defined as positive, if authors stated a benefit from the NIV therapy, negative, if they concluded a lack of benefit or identified significant adverse events or complications from the NIV therapy, neutral if they did not clearly state positive or negative conclusions, and indeterminate if reviewers were unable to classify authors' conclusions under other headings. Twenty percent of the extracted data were verified by a second reviewer for accuracy and completeness.

Data synthesis: Data were collated in order to present a narrative account of the existing literature (182, 183): The Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols 2015 statement was followed in the reporting of the results (184). Interpretations or

grouping of terms related to NIV therapies were avoided to ensure authors' original terms were preserved. For the data synthesis, MeSH terms (PubMed) were used to define a medical condition when authors used multiple terms to refer to the same medical condition to avoid overlapping. Medical conditions were then classified into disease categories attending to the underlying pathophysiology. Word cloud software (http://www.tagxedo.com) was used to produce qualitative syntheses of NIV terms and medical conditions.

Statistical analysis: SPSS version 24 (1989, 2016) was used for statistical analysis. Descriptive data were reported as absolute numbers and percentages and medians and ranges were calculated for quantitative variables. Age was provided as mean and standard deviation. Pearson Chi-Square or Fisher's exact test were used to calculate differences by subgroups such as age and disease category.

3.1.4. Results

We identified 11,581 potentially relevant studies; 289 are included in this scoping review (Figure 3.1). The majority of the studies were published as journal articles (74%, 215/289). The contributions from gray literature sources represented 26% of included studies (74/289) and these were predominantly conference abstracts (22%, 63/289). The first article on long-term NIV in children identified with our search strategy was published in 1992 with a median year of publication of 2011 (Figure 3.2). The majority of studies were conducted in North America (41%, 119/289) and Europe (36%, 104/289) (Figure 3.3). A total of 91 studies were excluded due to language: 53 from European countries and 38 from Asian countries.

Non-invasive ventilation terms

Seventy-six terms were used to describe NIV (Figure 3.4). The most common terms included non-invasive ventilation (NIV 22%, 65/289), non-invasive positive pressure ventilation (NPPV 12%, 35/289) and positive airway pressure (PAP 9%, 27/289). Different terms were also used to refer to specific NIV modalities including continuous positive pressure ventilation (CPAP 33%, 95/289), bi-level positive airway pressure ventilation (Bi-level 16%, 46/289) and auto-positive airway pressure (Auto-PAP 2%, 7/289).

Study design

Study designs (Table 3.1) were predominantly quantitative (91%, 263/289) with few qualitative (2%, 5/289), biomedical (6%, 17/289) and manufacturer reports (1%, 4/289). The most common quantitative study design was observational (63%, 182/289) including cohort studies (42%, 122/289), case-control studies (4%, 12/289), and case series (17%, 48/289). Twelve percent of studies (34/289) were cross-sectional surveys with 7% (19/289) randomized and non-randomized controlled trials and 10% (28/289) within subject interventional controlled before-after studies. The majority of studies were single center studies (84%, 244/289) with 16% (45/289) multicenter studies. Only 4% (2/45) of the multicenter studies were also multinational. Fifty-four percent (155/289) of the studies were retrospective. The overall median sample size of included studies was 14 (range 3-658). Multicenter studies had median sample size of 24 (range 6-658). Only 23% (66/289) of studies included a control or comparison group. Median study duration was 40 months (range 1-552 months); study duration for interventional studies, however, was shorter, with a median of 25 months (range 1-102). The duration of the NIV

intervention was only reported in 42% (122/289) of the studies. For the studies reporting NIV duration, the median duration of NIV use was 12 months (0-180 months).

Subject characteristics

NIV was used for a broad range of medical conditions (Figure 3.5). Seventy-three medical conditions were identified from the methods section of the included studies. The most common medical conditions reported included OSA (29%, 84/289), SMA (8%, 22/289), sleep disordered breathing (6%, 16/289), and NMD (5%, 14/289). When grouping medical conditions (Table 3.2), the majority of the studies investigated disorders of upper airway obstruction (33%, 94/289) or neuromuscular and other musculoskeletal disorders (22%, 63/289). Studies investigating NIV as a treatment for sleep disordered breathing in the context of childhood obesity were only published in the last 10 y, with the first study published in 2006. Over time, there has been an increasing proportion of studies focused on cohorts of children using long-term NIV regardless of the medical condition, with 73% (55/75) of the studies with this study design published in the last 10 y.

There was considerable variability in the age when NIV was started. The mean age of NIV initiation was 8.06 ± 3.08 y with the majority of the studies reporting data on children across a wide age span (0-24 y; Figure 3.6). Although 39% of the studies (114/289) included infants (under 2 y of age) in their target populations, only 9% of studies (27/289) were exclusively undertaken in this population. The medical conditions studied differed by age group (Fisher's exact test 102.820, $p<0.05$). In studies focused on infants, the predominant medical condition was upper airway disorders (52%, 14/27) followed by 33% (10/27) of studies focused on NMD (9 of which were on SMA type 1), 4% (1/27) on congenital central hypoventilation syndrome (CCHS), and 7%

(2/27) on multiple conditions. In studies that included children over 2 y of age (30%, 88/289), 41% (36/88) were focused on upper airway diseases, 20% (18/88) on NMD, 10% (9/88) on sleep disordered breathing related to obesity, 8% (7/88) on pulmonary disease, and 10% (9/88) on multiple diseases. The use of NIV for treatment of obesity related sleep disordered breathing and pulmonary diseases was only reported in older children. Conversely, the studies focused on multiple disease categories where data on age was reported (55/289) were mostly cohorts of children aged 0-18 y (78%, 43/55).

NIV equipment

CPAP use was reported in 25% (73/289) of studies compared to 21% (61/289) for bi-level therapies and 2% (7/289) for auto-PAP; 22% (63/289) of the studies reported data on combined CPAP and bi-level therapies and 20% (57/289) on disaggregated data for NIV and IMV therapies (Table 3.2). In 9% (27/289) of the studies, there is no specific description in the methodology of the non-invasive intervention used; that is, CPAP and/or bilevel were not specified. There was only one study reporting on NPV exclusively and 11 articles included NPV among other ventilator therapies.

There were differences in NIV type use according to the disease category (Fisher's exact test 166.164, $p<0.05$). Seventy-eight percent (62/79) of studies reporting on CPAP and auto-PAP included children with upper airway disorders, obesity or other medical conditions. Studies on bilevel therapies were focused on children with musculoskeletal diseases (48%, 29/61), cohorts of children including multiple medical conditions (18%, 11/61), and children with pulmonary conditions (16%, 10/61), with few reports in children with upper airway disorders (7%, 4/61). Studies reporting CPAP and bilevel interventions together were mostly done in children with

upper airway disorders (46%, 29/63) and cohorts of children including multiple medical conditions (33%, 21/63), with few reports in children with musculoskeletal diseases (11%, 7/63). Studies including NIV and IMV therapies together reported data mostly on cohorts of children with multiple medical conditions (54%, 31/57) and children with musculoskeletal diseases (21%, 12/57).

The interface type was only specified in 46% (132/289) of studies. In those where details of the interface were reported, nasal masks were most commonly used alone (52%, 69/132) or in combination with full face masks (20%, 27/132).

Outcomes of interest

A wide range of outcomes of interest was described. This included objective measurements (e.g., apnea-hypopnea index, blood gas measurements, oxygen saturation, validated questionnaire scores, adherence rate from NIV machine downloads) in 63% (182/289) of the studies, subjective information from medical letters (e.g. improvement on clinical symptoms reported by physician, adverse events) in 50% (145/289) of the studies, subjective data collected directly from patients and families in 10% (30/289), and surveys of health care providers asking for descriptive data of their patient populations, practice patterns or assessing their knowledge in 9% (27/289).

Descriptive data such as the number of patients initiated on NIV, patient characteristics and NIV discontinuation rates were reported on 61% (177/289), 51% (147/289) and 7% (20/289) respectively (Table 3.3). A variety of diagnostic tests to measure efficacy of NIV were used, which was most commonly data from sleep studies, including polysomnography (24%, 69/289) and polygraphy (2%, 6/289). Examples of measured outcomes from sleep studies were apnea-

hypopnea index, end tidal or transcutaneous carbon dioxide, oxygen saturation, sleep architecture, arousal index. A combination of home overnight pulse oximetry and transcutaneous carbon dioxide levels was reported in 1% (2/289) of the studies. In a smaller proportion, blood gas measurements (e.g. partial pressure of oxygen and carbon dioxide) were used (5%, 14/289) to measure efficacy of NIV. Fifteen percent (43/289) of the studies reported reduction of respiratory morbidity such as improvement of respiratory symptoms, tracheostomy avoidance or decannulation, or reduction in post-operative complications. Reduction of healthcare encounters related to respiratory exacerbations was reported in 5% (13/289) of the studies. Improvements of symptoms in other areas affected by sleep breathing disorders were not well described. For instance, improvements in sleep symptoms, neurocognitive outcomes, mood and behavior, and quality of life were reported in 5% or less (14/289, 13/289, 5/289 and 14/289, respectively) of studies. Mortality rates were an outcome of interest in 6% (18/289) of the studies. Ten percent of the studies (28/289) tested the efficiency of NIV technology either assessing NIV machine settings or interfaces.

Some of the outcomes of interest differed by disease category. Of 69 studies reporting outcomes from sleep studies (including polysomnography (PSG), polygraphy (PG) and limited channel studies), 54% (37/69) of studies were conducted in children with upper airway obstruction disorders, 22% (15/69) in children with musculoskeletal and neuromuscular diseases, and 14% (10/69) in cohorts combining children with multiple underlying conditions (Fisher's exact test 19.035, $p< 0.05$). Studies reporting data on mortality (6%, 18/289) were exclusively conducted in children with musculoskeletal and neuromuscular diseases (44%, 8/18) or cohorts of children with multiple underlying conditions (50%, 9/18) (Fisher's exact test 16.462, $p<0.05$).

Looking at studies reporting respiratory morbidity or reduction of health care encounters due to respiratory exacerbations (17%, 50/289), 24% (12/50) were in children with upper airway obstruction disorders, 38% (19/50) in musculoskeletal and neuromuscular diseases, and 26% (13/50) on children with multiple diseases, (Fisher's exact test 11.412, $p<0.05$). The proportion of studies reporting outcomes on sleep symptoms, mood and behavior, neurocognition and quality of life did not differ by disease category.

Adverse events were reported in 20% (59/289) of the studies. The most common complications found were skin lesions (e.g. irritation, redness, breakdown; 6%, 18/289), mask intolerance, leak or NIV therapy intolerance (5%, 15/289), nasal symptoms (e.g. congestion, rhinorrhea, epistaxis, sinusitis; 2%, 7/289), device failure (2%, 7/289), midface hypoplasia (2%, 6/289), abdominal distension (2%, 6/289), and death (2%, 5/289).

Adherence to NIV was reported in 26% (74/289) of the studies. Of note, while the first report on adherence was in 1992, the majority of studies reporting on adherence (77%, 57/74) were published in the last 10 y. Only 3% of the studies (10/289) analyzed data on treatment burden of long-term NIV for children and their caregivers.

Statistical analysis

Purely descriptive data were reported in 28% of the studies (81/289), while 63% of studies (182/289) were designed to measure differences in outcomes between groups or time points. Seven percent (21/289) of the studies reported only narrative data on NIV, including case series (4%, 12/289), qualitative studies (2%, 5/289), and manufacturer reports (1%, 4/289). There were ongoing interventional studies (2%, 5/289) for which data is not yet available.

Authors' conclusions

In the majority of studies, the authors stated a conclusion about NIV (96%, 278/289). Overall, 73% (203/278) of the studies included a conclusion that the long-term use of NIV in children may provide benefits while 4% (10/278) had a negative conclusion (i.e. no benefit of NIV or adverse events), 16% (45/278) were indeterminate, and 7% (20/278) neutral. In the studies where authors stated positive conclusions of NIV, 59% (119/203) authors performed statistical analysis to test for significant differences for at least one of their outcomes, with 30% of the studies (60/203) supporting their positive conclusions with descriptive data only and the remaining 7% (14/203) reporting narrative outcome data (Pearson Chi-Square 17.089, $p<0.04$).

3.1.5. Discussion

This is the first systematic overview of the literature on long-term NIV in children. The topic of this scoping review was intentionally broad with the goal of identifying the nature and extent of the literature relevant to long-term use of NIV in children. The results highlight the diversity of medical conditions for which long-term NIV has been reported and the variability of the information available to support its use across medical conditions. We also identified that the evidence for long-term NIV use differs by age group, with some medical conditions studied predominantly or exclusively in certain age groups. There is a paucity of multicenter, randomized, and interventional studies with predominantly descriptive results. While there are a range of outcome measurements studied to determine the benefits of NIV in children populations, there is less emphasis on other aspects of the NIV therapies such as treatment burden and most research available does not seem to be patient-prioritized. The results of this scoping review

provide a detailed analysis of the existing evidence supporting the use of long-term NIV in children.

We identified a variety of terms referring to the description of NIV therapies. Differences in terms appear to relate to the definition of the technology (e.g. positive airway pressure), the specific NIV modality (e.g. CPAP, bi-level, auto-PAP), the time of the day for NIV use (e.g. nocturnal ventilation), the type of interface used (e.g. nasal ventilation), or simply the author's preference. The meaning of certain terms was not always clear, presenting a challenge for identification of the relevant literature. For example, terms referring to the use of ventilatory support technology at home (e.g. home mechanical ventilation, long-term ventilation, domiciliary ventilation) often included both children on NIV and IMV or did not clearly define the type of interface. Based on our results, we would recommend the use of the term 'non-invasive ventilation' (abbreviated as NIV) to denote the use of methods of ventilatory support delivered with an interface outside the airway. Using this definition, CPAP, bi-level, auto-PAP and other modalities of delivering ventilatory support with an interface outside the airway are included as sub-types of NIV. This definition is consistent with the medical subject heading for NIV, used for indexing articles in PubMed which defines NIV as '*techniques for administering artificial respiration without the need of intratracheal intubation*' (http://www.ncbi.nlm.nih.gov/mesh/D063087). We recognize that CPAP is not considered by many to provide ventilation support; CPAP is, however, included under the MeSH term 'positive pressure ventilation' defined as 'a method of mechanical ventilation in which pressure is maintained to increase the volume of gas remaining in the lungs at the end of expiration, thus reducing the shunting of blood through the lungs and improving gas exchange', supporting our

recommendation that CPAP is a method of ventilatory support. In addition, CPAP can be used both with an invasive and non-invasive interface, so it is important to distinguish these treatment modalities. Our results show that other authors have reported trends and outcomes combining children using both CPAP and bilevel (15, 17, 18, 21). This makes sense given children using CPAP and bilevel therapies share common challenges related to adherence and complications with the non-invasive interface, similar methods of monitoring therapy and overlap in the outcome measures. Lastly, there is overlap in the medical conditions of children using CPAP and bilevel. While certain medical conditions are exclusively treated with bilevel therapy (e.g. CCHS), many others have pathophysiology that can be treated with CPAP or bilevel (e.g. upper airway obstruction, obesity). Other methods of NIV such as auto-PAP and NPV have been less well described in the literature. The use of the term NIV to refer to any ventilatory support administered through a non-invasive interface will simplify the literature search and allow clear differentiation from invasive methods of ventilation.

Starting in the 1980's, when the first case reports on long-term NIV use in children were published (11-13), there is substantial literature documenting the long-term use of NIV in children with a large variety of underlying conditions. Over the subsequent two decades, there has been a steady increase in the number of publications investigating the use of long-term NIV in children, with the greatest increase in the last 5 y. This pattern confirms the reported trends of increased use of long-term NIV worldwide (14, 15, 17-19, 21, 23, 24, 26, 27, 148, 165). The drivers of this increase in use are likely multi-factorial and include improvements in the technology for children using NIV, greater awareness of the potential use of NIV, as well as changes in funding for NIV. While there is an extensive literature on long-term NIV use in children,

there are clearly gaps in our understanding of the use of this technology, and a pressing need to fill these gaps in this growing field.

Our results highlight the low methodological quality of the literature in long-term NIV use in children. The majority of the available data comes from descriptive studies, with small sample sizes and a paucity of randomized controlled clinical trials. We identified many single-center descriptive studies with similar methodology where the combination of data would enable larger sample size to allow subgroup analysis. This could facilitate the identification of common characteristics of those children that benefit most from long-term NIV and improve the power to detect between group differences. Randomized trials may be challenging given that NIV is an accepted therapy for many medical conditions, hence calling into question the ethics of randomizing subjects to alternative therapies or placebo. However, before-after comparisons within the same subjects provide an assessment of risks and benefits despite lower rigor than randomization.

Despite evidence of long-term NIV use in a large number of medical conditions, the majority of the current literature is focused on a small number of diseases including OSA and NMD. While these conditions are likely the most common ones leading to NIV use, this focus limits the extrapolation of this information to children with other medical conditions. Efforts to apply further systematic review methods to summarize data examining studies addressing specific outcomes for these more common conditions or broader outcomes for less prevalent conditions would be of value. For example, prior systematic reviews on OSA have included aspects of diagnosis, comorbidities, and surgical treatment options (66, 181, 206, 207); a similar systematic review focused on adherence to NIV in OSA would be informative. Systematic review

or meta-analysis of long-term NIV outcomes for children with NMD such as SMA, or DMD would also provide stronger evidence than individual study results. While there has been a previous systematic review on nocturnal mechanical ventilation in patients with neuromuscular and chest wall disorders of all ages, data were not separated into IMV and NIV (179, 180). Other medical conditions where long-term NIV use has been described, such as CCHS, cystic fibrosis, obesity, trisomy 21, or craniofacial abnormalities, present different challenges for NIV where a systematic review could help clarify what is known and not known about specific outcomes related to NIV use in these conditions. Future research efforts focused on multi-centre studies or the development of national or multi-national patient registries may be the best means of developing robust data to support NIV use for less common medical conditions.

Few studies focus exclusively on infant populations. Infancy represents a time when both breathing and sleep control mechanisms are evolving and, therefore, is a unique physiological period distinct from older children (47). Studies on long-term NIV use for medical conditions with significant respiratory morbidity during the neonatal period, such as craniofacial disorders, laryngomalacia, SMA type 1, or CCHS, are almost exclusively descriptive (209-211). Long-term NIV use may be an alternative to IMV as many of these infants improve with time, allowing discontinuation of ventilatory support and preventing complications related to tracheostomy and IMV (69, 212). Future studies exclusive to infants or including infants as a distinct group should assess outcomes that emphasize the unique sleep and respiratory physiology of infancy and take into account normal developmental changes across infancy when considering the impact of long-term NIV use.

Specific gaps in the literature include some negative aspects of long-term NIV therapies. While approximately 20% of the studies identified report on adverse events and adherence rates, other relevant outcomes such as treatment burden or barriers to adherence for children and caregivers were included in only 3% of included studies. This means there are limited data on the impact of long-term NIV on children and their families. No studies examining funding or community supports for long-term NIV were identified. The paucity of studies exploring the experience of NIV from the child, family and community viewpoints is an important gap. As the use of long-term NIV requires a significant investment, both with respect to the work involved in using NIV and in some cases the financial cost, the lack of information on the child, family and community experience with long-term NIV may limit our ability to provide the best possible care.

This scoping review provides a comprehensive and exhaustive examination of the literature on long-term NIV use in children. However, there are several limitations that must be acknowledged. As with any systematic review methodologies, a publication bias towards studies conducted in English-speaking countries is likely due to limited resources for translation. In our case, research done in certain geographical areas of Europe and Asia may be underrepresented. However, no articles from Africa or South America were excluded for that reason. Limited resources for translation might have resulted in some selection bias during the full-text screening. We did not contact authors for clarification of information. While contacting authors would have filled gaps in our data extraction, this scoping review is intended to represent the information that is most easily accessible and, therefore, available to parents, clinicians, and policy makers to support decision making relevant to long-term NIV use in children. Our inclusive approach was deliberate and allows us to define the scope of the literature relevant to our topic.

However, it also limits our ability to summarize details of diverse methods and outcomes. As such, our results represent the first step in describing the literature relevant to long-term NIV use in children with work underway for further analysis of these important data in more detail.

3.1.6. Conclusions

This scoping review has mapped the existing literature on the long-term use of NIV in children. Long-term NIV use has been documented in a great diversity of pediatric patient groups and NIV modalities. However, most of the studies to date have been observational and descriptive in nature. While more robust information exists for some conditions, there is a paucity of data relevant to many pediatric populations currently using NIV. In addition, outcomes studied may not be those of highest priority for children using NIV and their families. The results of this scoping review provide a rigorous overview of the existing literature and a context on which to build a research agenda aimed at improving the lives of children using long-term NIV.

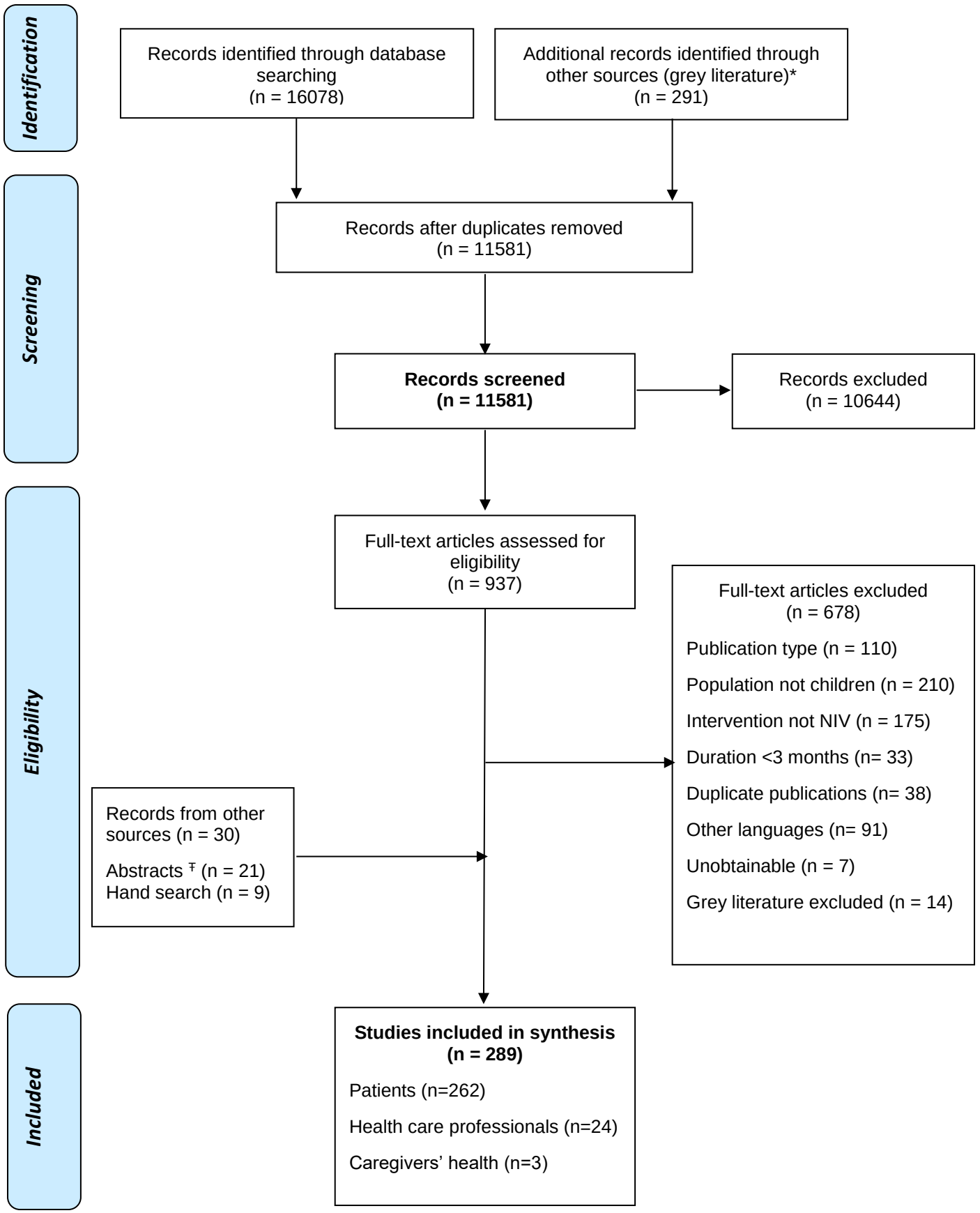
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 16078)
Additional records identified through other sources (grey literature)* (n = 291)
Records after duplicates removed (n = 11581)
Records screened (n = 11581)
Records excluded (n = 10644)
Full-text articles assessed for eligibility (n = 937)
Full-text articles excluded (n = 678)
Publication type (n = 110)
Population not children (n = 210)
Intervention not NIV (n = 175)
Duration <3 months (n= 33)
Duplicate publications (n= 38)
Other languages (n= 91)
Unobtainable (n = 7)
Grey literature excluded (n = 14)
Records from other sources (n = 30)
Abstracts ǂ (n = 21)
Hand search (n = 9)
Studies included in synthesis (n = 289)
Patients (n=262)
Health care professionals (n=24)
Caregivers' health (n=3)

Figure 3.1. Flow diagram of screened and included studies (adaption from PRISMA-P 2015).

* Each conference proceeding included is counted as a single record.

Ŧ Individual abstracts from conference proceedings have been added manually and duplicate data removed.

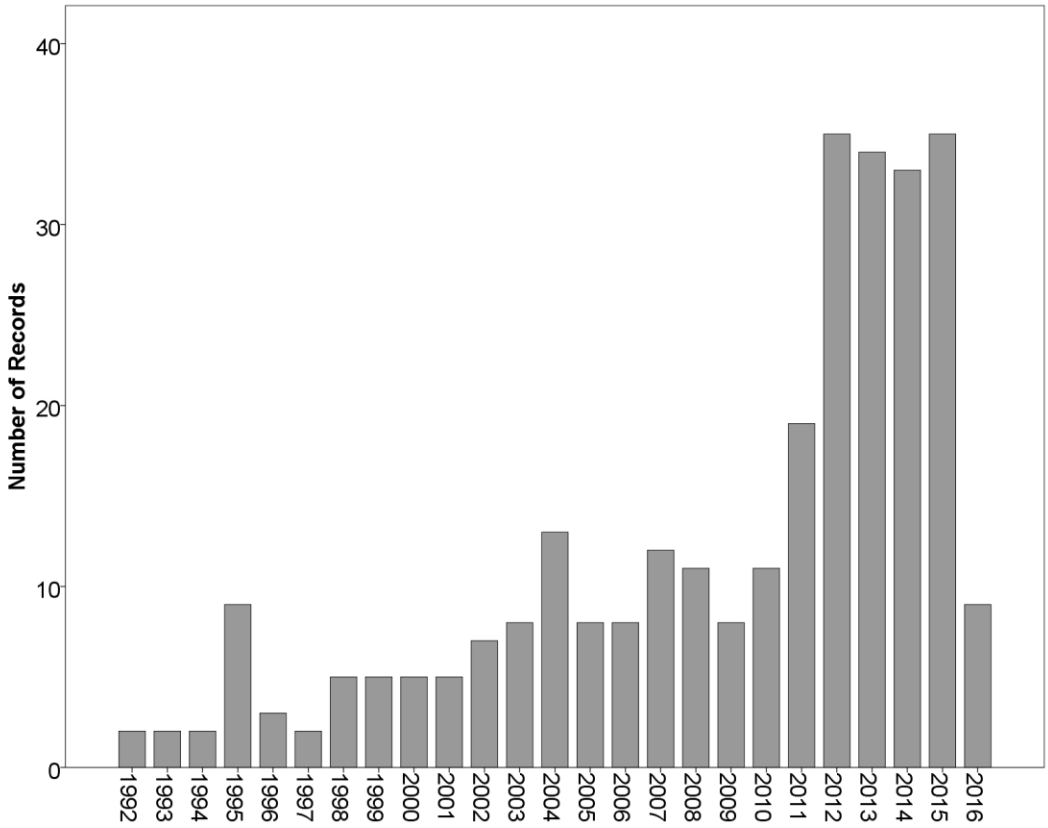

Figure 3.2. Number of publications by year of publication. The most noticeable increase in publications began in 2011. Publications for 2016 include only those published before 2 May 2016.

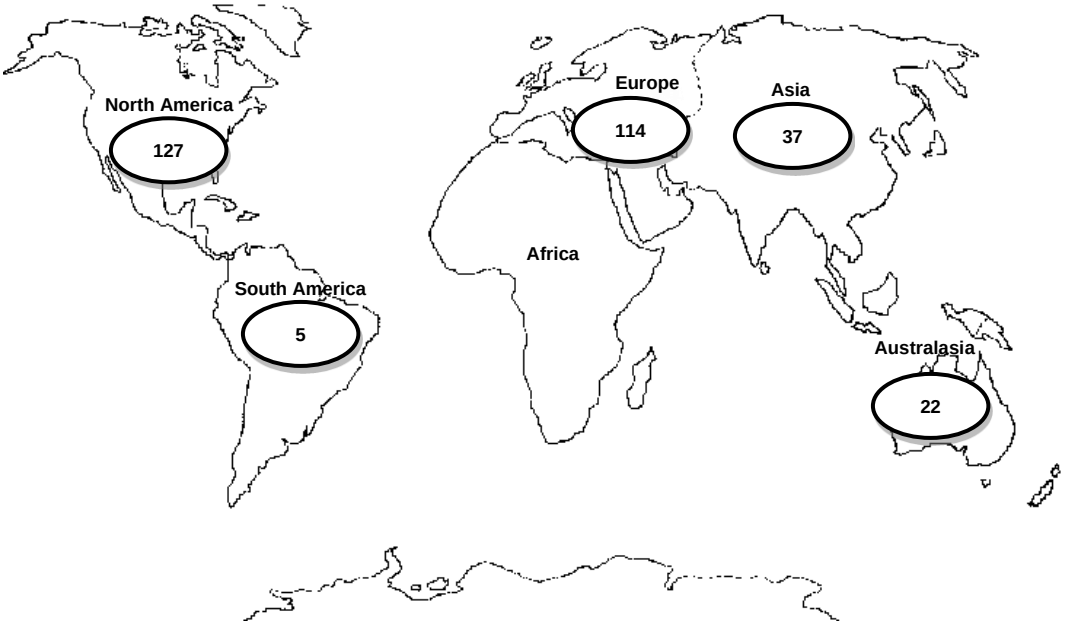

Figure 3.3. Geographical distribution of contributing authors. Publications with authors from multiple continents were counted in each contributing nation resulting in a higher total number than publications included.

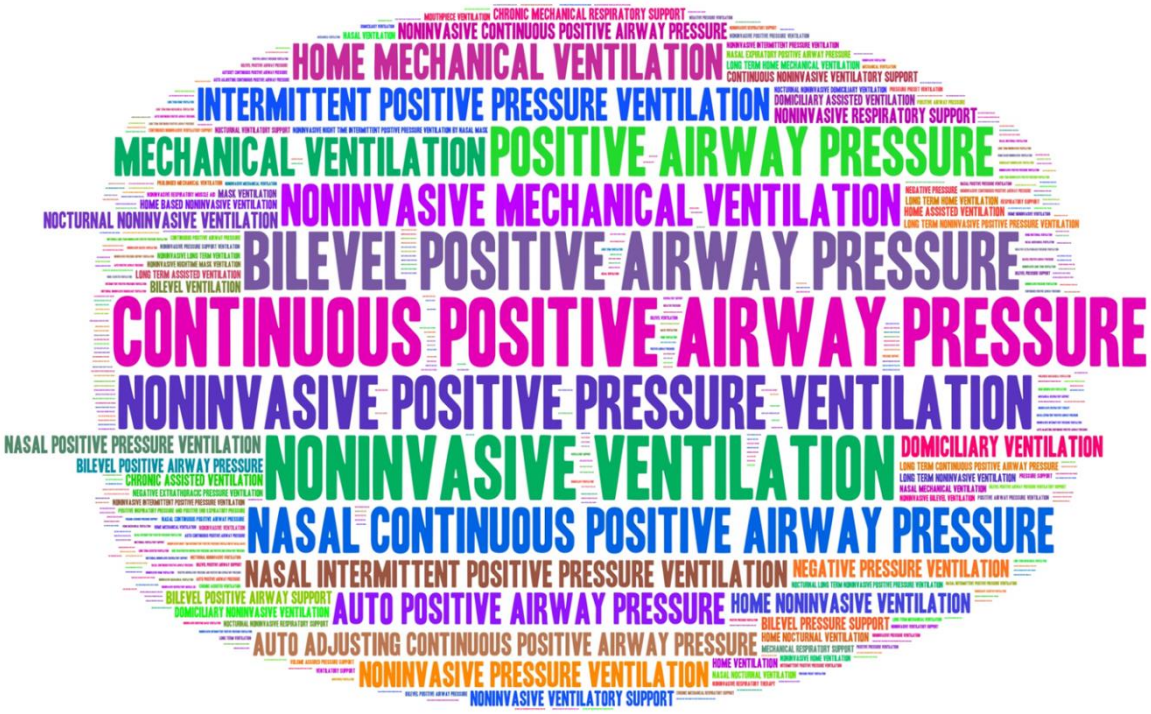

Figure 3.4. Word cloud created with tagxedo software summarizing 76 terms used to describe long-term non-invasive ventilation in children. The size of the words represents the frequency of the use of each term; larger words correspond to the terms that are used more frequently.

Figure 3.5. Word cloud with tagxedo software summarizing 73 medical conditions for which the use long-term NIV in children has been reported. The size of the words represents the frequency of the use of each medical condition; larger words correspond to the medical conditions with more reports of long-term NIV use in children. Share under creative copyright under a Creative Commons Attribution-Noncommercial-ShareAlike License 3.0 (https://creativecommons.org/licenses/by-nc-sa/3.0/us/).

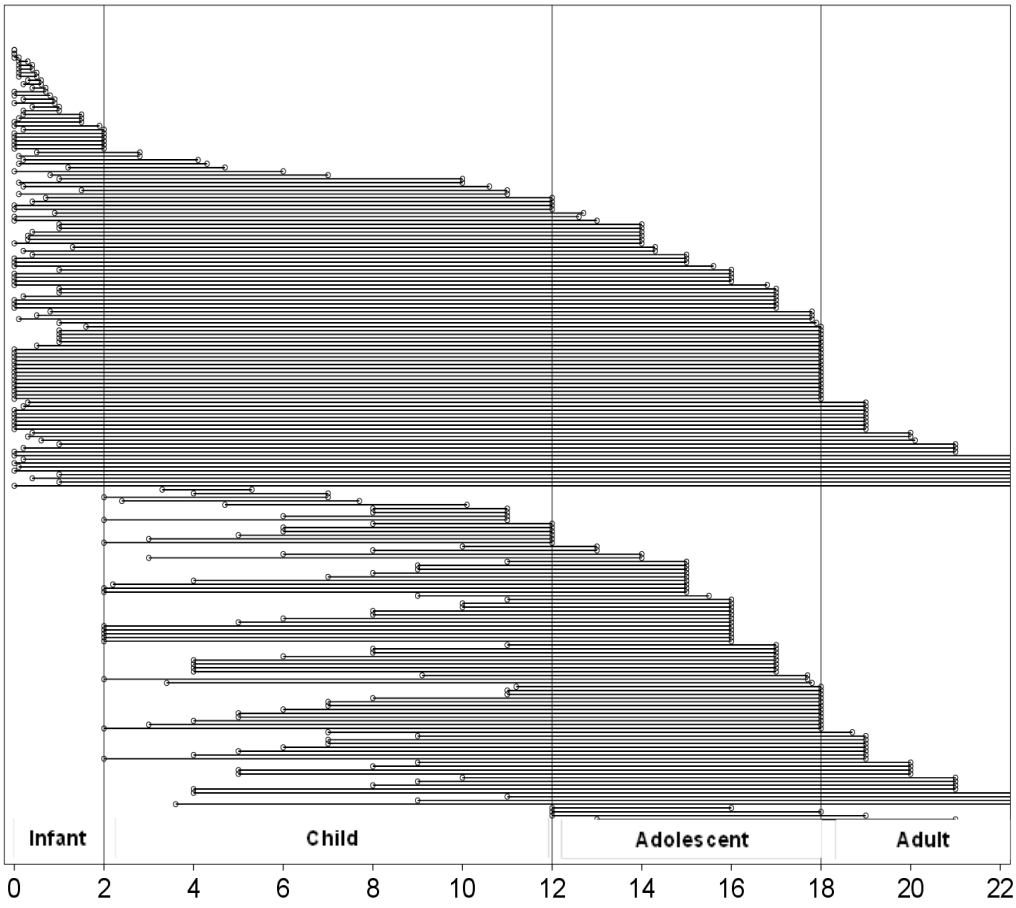

Figure 3.6. Age range in years of included in studies. Vertical axis markers at 2 year of age to indicate infancy, 12 y of age to indicate childhood, and 18 y to indicate adolescence. Each line represents one article.

Table 3.1. Summary of publication type and study design for 289 included studies. Numbers represent the number of studies with percentage in parentheses unless otherwise indicated.

Description	n (%)
Type of publication:	
Journal	215 (74)
Abstract	63 (22)
Dissertation	1 (1)
Manufacturer Report	4 (1)
Unpublished Trial	6 (2)
Type of study:	
Quantitative:	
Observational (Cohort, Case series, Case-Control)	182 (63)
Cross Sectional/Survey	34 (12)
Controlled Before-After	28 (10)
Randomized/Non-Randomized Controlled Trial	19 (7)
Qualitative	5 (2)

Bench Study	17 (6)
Manufacturer reports	4 (1)
Single vs multi-center:	
Single-center	244 (84)
Multi-center	45 (16)
Prospective vs retrospective:	
Prospective	134 (46)
Retrospective	155 (54)
Control group:	
Yes	66 (23)
No Treatment	29 (43)
Invasive Ventilation	13 (20)
Tonsillectomy and/or Adenoidectomy	5 (7)
Other	19 (31)
No	223 (77)
Number of study subjects using NIV (median, range)	14 (3-658)

Study duration (months; median range)	40 (1-552)
Duration of NIV intervention (months; median, range)	12 (0-180)

NIV, non-invasive ventilation.

Table 3.2. Subject characteristics and NIV interventions reported in 289 included studies. Numbers represent the number of studies with percentage in parentheses unless otherwise indicated.

Characteristics	
Age at NIV start (y) (mean ± SD)	8.06 ± 3.09
Disease category:	**n (%)**
Upper airway obstruction	94 (33)
Neuromuscular/ Musculoskeletal	63 (22)
Pulmonary	16 (6)
Obesity	9 (3)
CNS	8 (3)
Multiple medical conditions	75 (26)
Other medical conditions (including cardiac, syndrome)	10 (3)
Not reported	14 (5)
Type of NIV:	**n (%)**
CPAP	73 (25)

Bi-level	61 (21)
CPAP + bi-level	63 (22)
NIV not specified	27 (9)
NIV + IMV	57 (20)
Negative pressure ventilation	1 (1)
Auto-PAP	7 (2)
Time of NIV use:	**n (%)**
Day and Night	45 (16)
Night only	112 (39)
Day Only	2 (1)
Not Reported	130 (45)
Interface type:	**n (%)**
Nasal	69 (24)
Nasal + full face	27 (9)
Multiple	20 (7)
Other: Full face, mouth piece, negative pressure	6 (2)

Not reported	167 (58)
Author's conclusion:	**n (%)**
Positive	203 (70)
Negative	10 (4)
Neutral/Indeterminate	65 (23)
Not reported	11 (4)

Auto-PAP, auto positive airway pressure; CNS, central nervous system; CPAP, continuous positive pressure; IMV, invasive mechanical ventilation; NIV: non-invasive ventilation; SD, standard deviation.

Table 3.3. Summary of outcomes described in the 289 included studies. Numbers represent the number of studies with percentage in parentheses unless otherwise indicated.

Outcomes	n (%)
Descriptive data	
Number of patients initiated NIV	177 (61)
Patient characteristics	147 (51)
Discontinuation of NIV	20 (7)
Efficacy of NIV	
Sleep studies (including PSG, PG, limited channel studies)	77 (27)
Respiratory gases	14 (5)
Other respiratory tests (pulmonary function test, airway pressures, chest X-ray)	7 (2)
Metabolic outcomes	4 (1)
Other (echocardiogram, EEG)	4 (1)
Benefit from NIV	

Respiratory symptoms (airway obstruction, hypoventilation, postoperative complications, tracheostomy avoidance or decannulation) Reduction of health care encounters due to respiratory exacerbation Sleep Neurocognition Quality of life Mood/behavior Growth and development Increased survival Other symptoms	43 (15) 13 (5) 14 (5) 13 (5) 14 (5) 5 (2) 5 (2) 8 (3) 2 (<1)
Mortality rate	18 (6)
Adverse events	59 (20)
Compliance/ adherence	74 (26)
NIV machine settings and interfaces	28 (10)
Healthcare providers knowledge/ practice	7 (3)

Other (optimal pressure requirements, predictors of NIV need…)	19 (6)

NIV, non-invasive ventilation. PG, polygraphy. PSG, polysomnography. EEG, electroencephalogram.

CHAPTER 4: LONGITUDINAL CHANGES IN CLINICAL CHARACTERISTICS AND OUTCOMES FOR CHILDREN USING LONG-TERM NON-INVASIVE VENTILATION

4.1. INTRODUCTION

As clinicians and researchers, we have witnessed a change in in the clinical interventions available for critically ill children leading to more children requiring long-term NIV, as well as a rapid growth in the use of NIV technology in children with non-critical sleep-related breathing disorders. Further, our prior scoping review has reflected this change with growing number of publications since the early 2000s. These changes over time likely require adjustments of our interventions and available resources. With the purpose of analyzing changes in the characteristics of children in our cohort and NIV technology use over time, we used trend analysis to compare three different periods of time and establish a trend. As well, analyzed changes in long-term outcomes among the established epochs. The results of this work, presented in chapter 4, have been published in a relevant journal and presented in multiple national and international conferences with good acceptance.

Articles published as: Castro-Codesal ML, Dehaan K, Bedi PK, Bendiak GN, Schmalz L, Katz SL, MacLean JE. Long-term non-invasive ventilation in children: regional longitudinal trends and outcomes. PLoS One 2018; 13: 1 e0192111. DOI: 10.1371/journal.pone.0192111. eCollection 2018. Permission for data reproduction was obtained from the journal.

4.2. ARTICLE 3: LONGITUDINAL CHANGES IN CLINICAL CHARACTERISTICS AND OUTCOMES FOR CHILDREN USING LONG-TERM NON-INVASIVE VENTILATION

4.2.1. Abstract

Objectives: To describe longitudinal trends in long-term non-invasive ventilation (NIV) use in children including changes in clinical characteristics, NIV technology, and outcomes.

Methods: This was a multicenter retrospective cohort of all children started on long-term NIV from 2005 to 2014. All children 0 to 18 years who used NIV continuously for at least 3 months were included. Measures and main outcomes were: 1) Number of children starting NIV; 2) primary medical condition; 3) medical complexity defined by number of comorbidities, surgeries and additional technologies; 4) severity of sleep disordered breathing measured by diagnostic polysomnography; 5) NIV technology and use; 6) reasons for NIV discontinuation including mortality. Data were divided into equal time periods for analysis.

Results: A total of 622 children were included in the study. Median age at NIV initiation was 7.8 years (range 0-18 years). NIV incidence and prevalence increased five and three-fold over the 10-year period. More children with neurological and cardio-respiratory conditions started NIV over time, from 13% (95%CI, 8%-20%) and 6% (95%CI, 3%-10%) respectively in 2005-2008 to 23% (95%CI, 18%-28%) and 9% (95%CI, 6%-14%, p=0.008) in 2011-2014. Medical complexity and severity of the sleep-disordered breathing did not change over time. Overall, survival was 95%; mortality rates, however, rose from 3.4 cases (95% CI, 0.5-24.3) to 142.1 (95% CI 80.7-250.3, p<0.001) per 1000 children-years between 2005-2008 and 2011-2014. Mortality rates differed by diagnostic category, with higher rates in children with neurological and cardio-respiratory conditions.

Conclusions: As demonstrated in other centers, there was a significant increase in NIV prevalence and incidence rate. There was no increase in medical complexity or severity of the breathing abnormalities of children receiving long-term NIV over time. The mortality rate increased over time, maybe attributable to increased use of NIV for children with neurological and cardio-respiratory conditions.

4.2.2. Introduction

Non-invasive ventilation (NIV) is a method of ventilatory support that has increasingly been used for a range of respiratory and sleep disorders in children since the first reports in the 1980's (11-13). With technological advances in NIV, where positive pressure is delivered through an interface outside the airway, children and their families sometimes have an alternative to invasive ventilation, where positive pressure is delivered through an endotracheal or tracheostomy tube (194). Over the last two decades, the use of NIV has led to a 5-15-fold increase in the use of home mechanical ventilation worldwide, with worldwide prevalence ranging from 2.1 to 13.7/100,000 in children (14, 15, 17, 19-22, 24, 26). Today, NIV is considered the standard of care for a range of medical conditions leading to sleep disordered breathing and chronic respiratory insufficiency or failure with a greater proportion of those starting on home mechanical ventilation surviving to adulthood (15, 104).

While the efficacy of long-term NIV for many underlying conditions is well established (104), information documenting the expanded use of this technology worldwide is limited to cross-sectional studies or single-centered cohorts (14, 15, 17-21, 23, 24, 26, 27, 148). Moreover, most of the aforementioned studies describe the increase in use with very little information about trends of clinical characteristics, NIV technology and use, or discontinuation rates. Multi-centered studies measuring longitudinal outcomes of long-term NIV programs are lacking. The objectives of this longitudinal multi-centered study are to: (1) describe the longitudinal trends of pediatric long-term NIV use over a 10-year period; and (2) examine the changes in clinical characteristics, NIV technology use, and long-term outcomes including NIV discontinuation and mortality rates. We hypothesized that, as NIV use has become more common, there has been a

greater diversity, higher complexity, and increased severity of sleep disordered breathing in children receiving NIV. Understanding the changes in NIV use over time will help us determine the best use of this technology and plan for future health care needs.

4.2.3. Materials and methods

Study design

This multicenter, regional, longitudinal population study examined children using long-term NIV in the province of Alberta and surrounding provinces between January 2005 and December 2014. The two tertiary care children's hospitals in the province, the Stollery Children's Hospital (Edmonton) and the Alberta Children's hospital (Calgary), participated in the study. As these hospitals also house the only government funded pediatric sleep laboratories, our cohort represents the majority of, if not all, children using NIV in the province of Alberta. These programs also provide care for children in surrounding provinces, including the Northwest Territories, and parts of Saskatchewan, British Columbia, and the Yukon.

The study protocol was approved by the Health Research Ethics Board (HREB) at the University of Alberta and the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary. As this was a retrospective study, our research ethics board waived the need for consent from participants and legal guardians. Subject identifiers were collected to enable data matching, but subjects were assigned a subject number during the data extraction and identifiers were stored separately from the research data. Data was stored in a secure REDCap electronic database (213).

Measures of interest

Changes in the following measures were assessed: 1) Incidence and prevalence of children on long-term NIV; 2) Primary medical conditions; 3) Medical complexity of children defined by the total number of comorbidities, surgeries, and use of additional technologies; 4) Severity of sleep disordered breathing measured by diagnostic polysomnography (PSG); 5) NIV technology use; and 6) Reasons for NIV discontinuation including mortality.

Subjects

Subjects included all children aged 0 to 18 years receiving NIV in a non-acute care setting for at least 3 months continuously. We defined NIV as any mode of ventilatory support where positive pressure is delivered through an interface outside the airway, including continuous positive airway pressure (CPAP), auto positive airway pressure (auto-PAP) and bi-level positive airway pressure (BPAP) therapies. Subjects were identified through the hospital records of the NIV programs at the two participating hospitals for all children referred for NIV initiation.

Data collection

Data collection included review of medical charts and sleep laboratory records. Data on ethnicity were self-reported by patients/parents at one centre, and physician reported at the other. Demographics, primary diagnoses, chronic comorbidities, any surgery performed prior to NIV initiation that was documented in the medical chart (tympanostomy tubes and dental restoration were excluded from the analysis), and other additional technologies in use were collected at the time of NIV initiation. The primary conditions leading to the need for NIV initiation were grouped into five broad diagnostic categories: central nervous system (CNS), upper airway (UA), cardio-respiratory (Cardio-Resp; excludes UA), musculoskeletal and

neuromuscular (MSNM) disorders, and unclassified conditions. Children with multiple medical conditions were grouped as 'unclassified' if it was not possible to identify the specific medical condition leading to NIV initiation. Any other chronic co-occurring medical diagnoses documented in the chart were considered comorbidities. Data extracted from the diagnostic PSG or the diagnostic portion of a split PSG, including the number of apneas and hypopneas per hour of sleep, oxygen saturation and carbon dioxide levels, were used to assess the severity of the sleep disordered breathing. Data on NIV initiation included NIV technology and settings, interface type, triggers for starting NIV, location for NIV initiation, and number of used hours. Compliance data, including the number of nights with use for more than 4 hours and average number of hours per night, was extracted from NIV machine downloads. Reasons for NIV discontinuation and total duration of NIV in those children discharged from the NIV programs were collected at the most recent visit.

Statistical analysis

Descriptive statistics summarized patient characteristics, NIV technology and reasons for NIV discontinuation. Incidence rate (per 100,000 children per year) and prevalence (per 100,000 children) for children living in Alberta over a 10-year period were calculated using data available from Census Canada on the number of children 0-19 years of age (214). Changes in NIV annual incidence rate were calculated using permutation tests for joinpoint regression model (215). For the rest of the trend analysis, data were divided into three equal 3.3-year epochs (2005-2008; 2008-2011; 2011-2014) to calculate differences over time. Kruskal-Wallis test was used to compare differences in medians of non-normally distributed variables over time. Post hoc Bonferroni correction was applied for multiple comparisons. Pearson Chi-Square and Fisher's

Exact Test were used to assess differences between categorical variables. Trend analysis was used to calculate trends in outcome rates over time. Survival curves and log-rank test were used to estimate differences in survival by diagnostic category. Hypothesis tests were 2-sided and statistically significant differences between groups were documented by $p < 0.05$. SPSS version 24.0 (1989, 2016), STATA v13 (STATA, 2013) and the Joinpoint Regression Program (REF) were used for statistical analysis.

4.2.4 results

Description of patient characteristics

A total of 891 records were reviewed; 216 children used NIV for less than three months or were older than 18 at NIV start, and 51 charts were unavailable. The analysis included 622 children (61% male) of whom 87% were living in Alberta (Table 4.1). The median age at NIV initiation was 7.8 y (0-18 y) with 18% of children <2 years, 16% from 2 to 4.9 years, 29% from 5 to 11.9 years and 29% over 12 years. The most common ethnicity (data available for 387 children) was Caucasian (268, 69%) followed by Aboriginal (45, 12%), Asian (40, 10%), African (17, 4%), Latin American (6, 2%), and mixed ethnicity (11, 3%). UA was the most common diagnostic category (60%) followed by CNS (17%). Details of the underlying conditions are available in Table 4.2. One or more comorbidities were identified in 92% of children. After adeno ± tonsillectomy, gastrostomy tube and/or fundoplication were the most common surgery prior to starting NIV. One or more additional technologies were used by 25% of children.

Description of NIV technology, use and discontinuation

CPAP was the most common NIV type (75%) followed by BPAP (22%) and auto-PAP (1%). Of the 550 children (88%) where data on mask interface was available, 62% of them used a nasal interface, 37% a full-face mask, and 1% other interfaces (i.e. total face mask, nasal pillows). NIV was started electively (before or after a PSG) for 83% of children, while 16% started during an acute illness, and 1% due to forced vital capacity below 30%, change from invasive ventilation to NIV, or as part of palliative care treatment. The majority of children started NIV at home (82%) with 18% starting in hospital. NIV was used primarily during nocturnal sleep (86%) followed by during nocturnal sleep and naps (9%), and for sleep and wake times (5%). Median airway pressure for CPAP was 7 (range 4-20) mmHg and median inspiratory and expiratory pressures for BPAP were 15 (range 8-22) mmHg and 6 (range 4-15) mmHg respectively with back-up respiratory rate of 16 (range 0-30) breaths/min. By the end of the study period in December 2014 (760 person-years; median follow-up period was 27 months, range 3-118), 46% of children had continued NIV, 39% discontinued NIV, 14% were transferred to adult services or other respiratory clinics, and 1% was lost to follow-up. For the children that discontinued NIV, the median duration of NIV prior to discontinuation was 21 (range 3-105) months. Reasons for NIV discontinuation were improvement in the underlying condition (16%), patient or family decision to stop therapy (15%), death (5%), switch to IMV (1%), or other reasons (3%). Other reasons included physician recommendation due to interaction with other therapies (i.e. oral appliance or maxillary-facial surgery) or physician recommendation due to poor quality of life. The median age at death was 3.4 y (range 0.25-20.9 y); the primary medical conditions of children who died are presented in Table 4.3.

Longitudinal trends in incidence and prevalence of NIV

Annual NIV incidence rate (excluding children from other provinces) increased significantly each year during the period 2005-2008, from 1.65 per 100,000 children started on NIV in 2005 to 8.01 in 2008 and then stabilized at 7.9 per 100,000 children started on NIV per year during the periods 2008-2011 and 2011-2014 (Regression joint point model, $p<0.001$; Figure 4.1). The number of children transferred to adult services increased over time, with a median of zero (range 0-1) children/y between 2005-2008, two (range 0-9) children/y between 2008-2011, and four (range 5-19) children/y between 2011-2014 (Kruskal-Wallis test, $p<0.001$). Post hoc analysis revealed differences between 2005-2008 and 2011-2014 (adjusted $p=0.01$). Because of changes in incidence and discharge rates, the prevalence rose from 10.3 children on NIV (95% CI, 10.2 to 10.3) per 100,000 children in the period 2005-2008 to 27.2 (95% CI, 27.1 to 27.3) in the period 2008-2011, to 27.9 (95% CI, 27.8 to28) in the period 2011-2014 (Kruskal-Wallis test, $p=0.007$), with post hoc analysis demonstrating an increase in prevalence between the periods 2005-2008 and 2011-2014 (adjusted $p=0.005$).

Longitudinal trends in patient characteristics

The proportion of children in each disease categories changed across epochs, with a higher proportion of children with CNS and Cardio-Resp conditions in the period 2011-2014, and a drop in the proportion of children with MSNM conditions (Table 4.4). The proportion of children who had adenoidectomy and/or tonsillectomy prior to starting NIV decreased over time. Age, number of comorbidities, other surgeries, additional technologies, and respiratory parameters on the initial diagnostic PSG did not change by epoch. Post doc subgroup analysis by diagnostic category showed no changes in the number of comorbidities, surgeries, additional technologies

and respiratory parameters of the PSG over time (data not shown), except for mean SpO2 in children with CNS conditions, with values of 94.5, 96 and 94.6% in each epoch respectively (Kruskal-Wallis, p=0.026).

Longitudinal trends in NIV technology and use

The use of nasal masks increased, with a concomitant decrease in full face masks over time (Table 4.5). Median CPAP pressure increased while BPAP inspiratory positive airway pressure and respiratory rate decreased over time. NIV use during sleep versus sleep and awake did not change over time. Indication and location for NIV initiation as well as the NIV mode were not different across epochs.

Compliance data did not change across epochs (Kruskal-Wallis, p=0.7), with no changes in the percentage of nights with NIV use above 4 hrs (median of 75%, range 0-100%) or in the total number of NIV hours (median 7hrs, range 0.3-20).

Longitudinal trends of outcomes

The number of children who died while using NIV increased over time, with mortality rates that went from 3.4 cases (95%CI, 0.5 to 24.3) per 1000 children started on NIV-years in 2005-2008 to 39.2 (95%CI, 23.6 to 64.9) in 2008-2011 and 142.1 (95%CI, 80.7 to 250.3) in 2011-2015 (Table 4.6, adjusted by age at NIV initiation). No changes in age at death occurred over time (Kruskal-Wallis, p=0.3), with median age of death of 18 years for the single child that died in 2005-2008, 3 years (0.25-20) in 2008-2011 and 4 years (0.8-17.8) in 2011-2014. NIV discontinuation rates due to improvement of the underlying condition, patient/family decision to stop NIV, and transfer to adult services increased over time. There was no change in the rate of children switched to invasive ventilation over time.

Subgroup analysis showed that survival curves differed by diagnostic category with lower survival in children with Cardio-Resp and CNS conditions, compared to MSNM and UA conditions (Fig 4.2). Mortality rate increased over time for children with CNS conditions, while mortality rates for other diagnostic categories did not change (Table 4.7).

4.2.5. Discussion

This study describes changes in the incidence, patient characteristics, technology use, and outcomes for a large multicenter cohort of children using long-term NIV. The results demonstrate that the incidence and prevalence of children using long-term NIV grew almost by five and three-fold respectively over the first years and plateaued afterwards. The medical conditions of children using long-term NIV changed with an increase in the total number and proportion of children with CNS and Cardio-Resp conditions and a decrease in the proportion of children with MSNM disorders. Neither medical complexity, defined as the number of chronic comorbidities and additional technology use, nor the severity of sleep disordered breathing by PSG parameters changed over time. Changes in NIV technology included a higher proportion of children using nasal masks, and minimal changes in both airway pressures and respiratory rate. While overall survival in this pediatric cohort was high at 95%, there was an increase in mortality rates for children using long-term NIV over time that may be attributable to the increase in the proportion of children with CNS and Cardio-Resp conditions starting long-term NIV. NIV discontinuation rates due to improvement of the underlying condition, decision to stop therapy, and transfer to adult services also increased over time.

The continued growth in the use of long-term NIV in children has been reported by groups around the world (14, 15, 17, 19-21, 26). Factors contributing to this increase likely include improvements in the available technology, progressive experience with this technology amongst healthcare providers, and increased use in children surviving critical conditions (28, 104, 118). A high rate of survival, also seen in our cohort, is likely to contribute to on-going increases in the prevalence of this population and more resources needed to provide medical care, consistent with reports by other groups (15, 21, 93). These trends are relevant not only to pediatric care but to the provision of adult healthcare services given the high likelihood of transition into adulthood.

Medical complexity and severity of sleep disordered breathing did not change over time in our cohort; this could be because children requiring long-term NIV are a priori a medically complex group. Definitions of children with medical complexity include children with significant chronic conditions affecting multiple body systems, progressive conditions associated with deteriorating health with limitations on life expectancy, continuous dependence on technology for at least 6 months, and malignancies that affect life function, with additional consideration of factors such as healthcare needs and usage, social and health system factors, and functional limitations (30, 216, 217). In our cohort, almost all children had at least one additional comorbidity, one quarter were supported by one or more additional technology, and only 16% ceased NIV because of improvement, suggesting that a substantial portion of these children are medically complex. Children with medical complexity have higher healthcare utilization, longer hospital lengths of stay, higher attributable healthcare costs, and impact on families including sleep deprived parents/caregivers, and financial and social hardships (29, 31-35). Applying the frameworks of medical complexity to children using long-term NIV may be useful to differentiate

both needs for care, relevant outcomes, and anticipated trajectories, including survival, for those with and without medical complexity.

While the overall rate of survival is high in our cohort, the increase in mortality across epochs is concerning. Despite there have not been significant changes in the overall level of complexity, severity of the sleep disordered breathing, and age at NIV initiation or death, mortality rate has grown. Interestingly, children that died while using NIV were on average younger than the median age for NIV initiation (3.4 vs 7.8 y), perhaps highlighting that younger children requiring NIV represent a distinct population. Our subgroup analysis confirmed increasing mortality trends for children with CNS conditions, which might be attributable to more children with these conditions starting on long-term NIV over time and lower survival. Children with Cardio-Resp conditions seem to show the same trend with an increasing number of children initiating NIV and lower survival curves. We did not demonstrate increasing medical complexity or clinically relevant changes in severity of sleep disordered breathing in both children with CNS or Cardio-Resp conditions. This may be because these have not changed or that our measures, including the fact that we did not categorize the severity of the underlying medical condition leading to NIV, were unable to capture changes in severity of medical illness. Multicenter prospective studies that allow larger sample size are indeed needed to confirm mortality rate and survival patterns. Two other cohorts reported on mortality rates by underlying medical condition. In one, after exclusion of children with neuromuscular diseases followed into adulthood, the highest mortality rate was in children with cardiac surgery, chronic lung disease, and 'other' conditions which include CNS conditions (15). In the second, of 11 reported deaths, 4 (36%) were in children with lower airway or CNS conditions (20). While there may be benefits of

long-term NIV other than survival, counseling with respect to survival should differ by medical condition. Prospective tracking with systematic collection of outcomes beyond survival are needed to better define the benefits and risk for the use of long-term NIV in specific medical conditions in children.

In addition to an increase in mortality over time, NIV discontinuation for other reasons also rose; the explanation for these increases remains unclear. NIV discontinuation due to improvement of the underlying condition has been described previously, with higher likelihood to discontinue NIV in children with UA or chronic lung diseases compared to MSNM disorders (17, 19-21, 24). No prior reports described a trend in NIV discontinuation because of family/patient decision to stop therapy for comparison with our results. Understanding the factors associated with improvements as well as decision to stop NIV will provide important information to children and their families for decision making at the time of initiation of long-term NIV.

There are some limitations of our study that must be acknowledged. Given the retrospective study design, data collection was limited to data available in the medical charts; if information on comorbidities or additional therapies was not documented, these may be underestimated in our cohort. Missing data, however, did not differ by diagnostic category or epoch so is unlikely to explain the reported trends. We defined long-term NIV as a minimum of three months use which excluded children who had difficulty initiating NIV. While we agree that the children who fail to initiate NIV are an important group to understand, a prospective study is needed to identify the characteristics of this group of children. Mortality rates reflect those

children who expired while using NIV as those who discontinued for other reasons were not followed.

4.2.6. Conclusions

This multicenter longitudinal study highlights the growing number of children receiving long-term NIV, consistent with trends worldwide. It demonstrates a greater use of long-term NIV in children with underlying CNS and Cardio-Resp conditions and small changes in technology use. Though overall survival remains high, an increase in mortality rate may be attributable to the shift in the underlying medical condition of children initiating long-term NIV and highlights differences in survival by diagnostic category. Children using long-term NIV likely have a high rate of medical complexity that has not changed over time. Additional understanding of the components of medical complexity, including healthcare usage and impact of families, will help to inform the care and resources needs as well as to set standards for the use of long-term NIV in children.

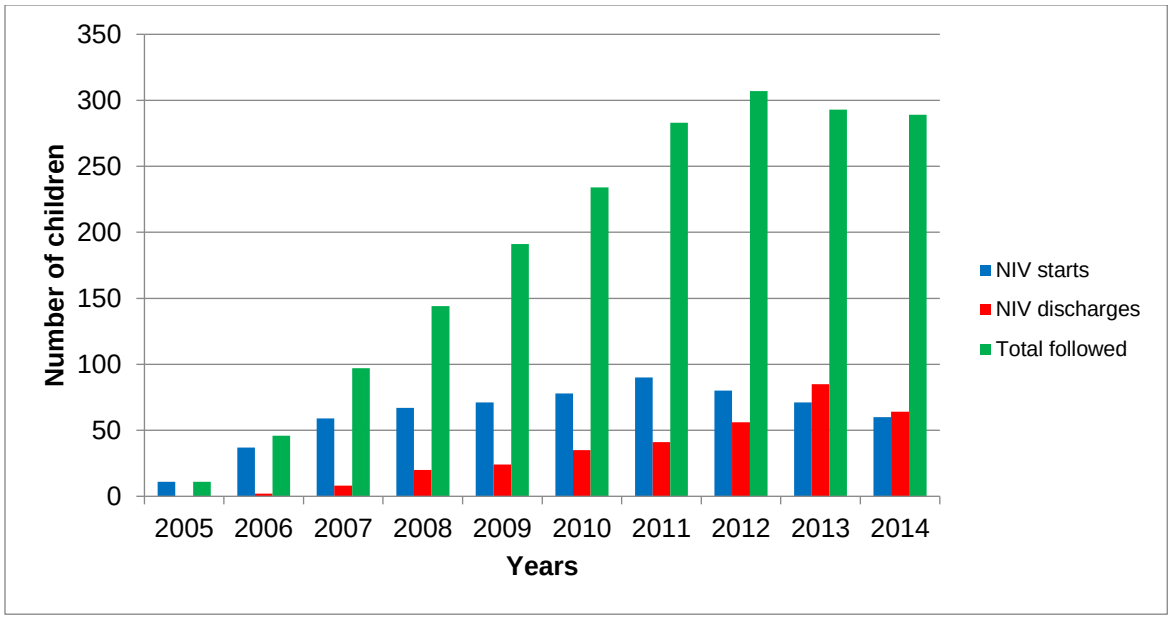

Figure 4.1. New NIV starts, discharges and total number of children followed by the NIV programs. NIV, non-invasive ventilation.

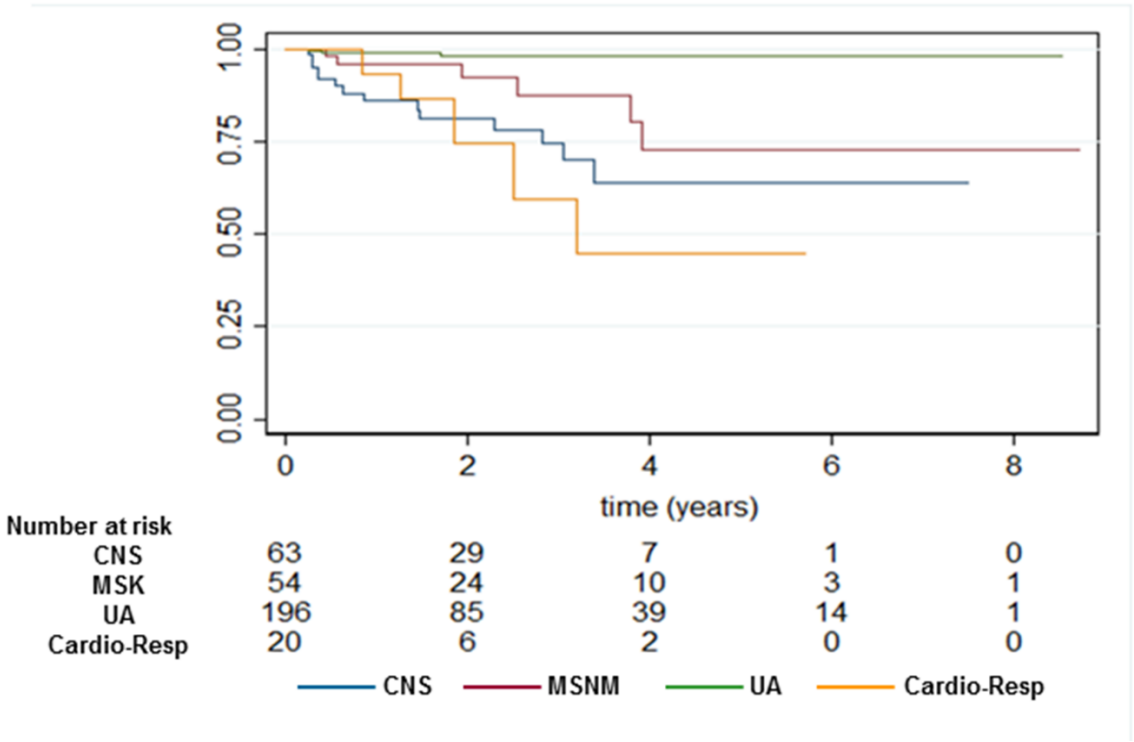

Figure 4.2. Kaplan-Meier survival curves in children on long-tern NIV by diagnostic category. Category "Unclassified" was excluded because there were no deaths in this group. There were significant differences in survival curves by diagnostic category (Log-Rank test, $p<0.001$). Indicated below, the number of children at risk for death within each diagnostic category per year.

Table 4.1. Clinical characteristics of 622 children started on long-term non-invasive ventilation.

Patient characteristics	**n=622** **n (%); median (range)**
Diagnostic category	
UA	371 (60)
CNS	107 (17)
MSNM	93 (15)
Cardio-Resp	39 (6)
Unclassified	12 (2)
Number of comorbidities	
0	50 (8)
1-2	310 (50)
3-4	161 (26)
5 or more	101 (16)
Surgeries prior to starting NIV	

AT/ adenoidectomy / tonsillectomy	300 (48)
G-tube and/or fundoplication	90 (15)
Neurosurgery	52 (8)
Cardiac	50 (8)
Upper airway	41 (7)
Spinal	21 (3)
Tracheostomy	19 (3)
Orthognathic surgery	8 (1)
Additional technologies	
G-tube/ NG tube feeding	99 (16)
Wheelchair	63 (10)
Daytime oxygen	30 (5)
V-P shunt	17 (3)
Pre-NIV diagnostic PSG [a]	
AHI, events/hour	11.2 (0-238)

Mean SpO_2, %	94.8 (64-99.9)
Mean $ETCO_2$, mmHg	44.7 (30.4-72.4)
Mean $TcCO_2$, mmHg	44.6 (32-99.3)

AHI, Apnea-Hypopnea index; AT, adenotonsillectomy; Cardio-Resp, cardio-respiratory (excludes UA); CNS, central nervous system; $ETCO_2$, end-tidal carbon dioxide; G-tube, gastrostomy tube; MSNM, musculoskeletal and neuromuscular; NG, nasogastric; PSG, polysomnography; SpO_2, pulse oxygen saturation; $TcCO_2$, transcutaneous carbon dioxide; UA, upper airway; V-P, shunt, ventriculo-peritoneal shunt.

[a] Data available for 547 (87%) children.

Table 4.2. Diagnostic categories and disease subgroups leading to initiation of non-invasive ventilation (adapted from Wallis, 2011) (26).

Diagnostic categories (%)	Disease subgroup	n=622
Central Nervous System (17%)	Congenital brain lesion	50
	Acquired brain injury	12
	Brain tumor	11
	Metabolic disease	8
	Congenital central hypoventilation syndrome	6
	Other central causes	20
Musculoskeletal and neuromuscular (15%)	Congenital myopathies	33
	Achondroplasia	17
	Duchenne muscular dystrophy	16
	Spinal muscular atrophy type 1, 2, 3	11
	Other muscular dystrophies	6
	Myelomeningocele	5

	Mucopolysaccharidosis	5
Upper airway (60%)	Obesity	119
	Down syndrome	111
	Obstructive sleep apnea	56
	Upper airway narrowing/malformation	35
	Airway malacia	32
	Craniosynostosis	7
	Prader Willi	11
Cardio- respiratory (6%)	BPD	13
	Chronic lung disease	10
	CHD	6
	Pulmonary hypertension	4
	Cystic fibrosis	3
	Cardiac failure	3
Unclassified (2%)	Chromosomal abnormality	4
	Diaphragmatic hernia and brain injury	1

	Fanconi syndrome	1
	Albright hereditary osteodystrophy	2
	BPD, CHD and myopathy	1
	Ectodermal dysplasia	1
	Diagnosis not available	2

Children with multiple medical conditions were allocated to a specific diagnostic category according to the medical condition that required non-invasive ventilation. If it was not possible to identify the specific medical condition leading to NIV initiation, children were grouped as 'unclassified'. BPD, bronchopulmonary dysplasia; CHD, Congenital heart disease.

Table 4.3. Summary of deaths in children using non-invasive ventilation by diagnostic categories.

Diagnostic category, n deaths/total n (%)	**Specific disease**	**n=28**
Central Nervous System n=14/107 (13%)	Congenital brain lesion	8
	Metabolic disease	3
	Brain tumor	1
	Congenital central hypoventilation	1
	Lennox-Gateaux syndrome	1
Musculoskeletal and neuromuscular n= 6/93 (6%)	Congenital myopathy	2
	Duchenne muscular dystrophy	2
	Spinal muscular atrophy type 1	1
	Spinal muscular atrophy type 2	1
Upper airway n=3/371 (1%)	Down syndrome	1
	Obstructive sleep apnea	1
	Pfeiffer syndrome	1

Cardio-respiratory n=5/39 (13%)	Congenital heart disease	3
	Cystic fibrosis	1
	Cardiac failure	1

Table 4.4. Longitudinal trends in the clinical characteristics of children using long-term non-invasive ventilation.

Clinical characteristics	**Epoch 1** **Jan 2005-Apr 2008** **(n=127)**	**Epoch 2** **May 2008-Aug 2011** **(n=262)**	**Epoch 3** **Sept 2011-Dec 2014** **(n=233)**	***P*** **value**
Age [a], median (range), yrs.	7.5 (0.2-17.9)	8.2 (0-18)	7.8 (0-17.8)	0.90
Diagnostic category [b]**;** n, %				
UA	80, 63 (95%CI 54-71)	161, 61 (95%CI 55-67)	130, 56 (95%CI 50-62)	0.34
CNS [c]	17, 13 (95%CI 8.5-20)	37, 14 (95%CI 10-18)	53, 23 (95%CI 18-28)	**0.02**
MSNM [d]	21, 17 (95%CI 11-24)	49, 19 (95%CI 14-24)	23, 10 (95%CI 7-14)	**0.01**
Cardio-Resp [e]	7, 6 (95%CI 3-10)	10, 4 (95%CI 2-7)	22, 9 (95%CI 6-14)	**0.03**
Unclassified	2, 2 (95%CI 0.4-5)	5, 2 (95%CI 0.8-4)	5, 2 (95%CI 0.9-5)	1
Comorbidities [b]; n, %				
0	12, 9 (95%CI 6-16)	18, 7 (95%CI 4-11)	20, 9 (95%CI 6-13)	0.64
1-2	57, 45 (95%CI 37-54)	138, 53 (95%CI 47-59)	115, 49 (95%CI 42-55)	0.34
3-4	39, 31 (95%CI 23-39)	66, 25 (95%CI 20-31)	56, 24 (95%CI 19-30)	0.37
5 or more	19, 15 (95%CI 10-22)	40, 15 (95%CI 11-20)	42, 18 (95%CI 13-24)	0.59

Surgeries [b]; n, %				
AT/Adenoidectomy [f]	74, 58 (95%CI 50-67)	133, 51 (95%CI 45-57)	88, 37 (95%CI 32-44)	**<0.001**
Other surgeries	50, 39 (95%CI 31-48)	96, 37 (95%CI 31-43)	85, 37 (95%CI 31-43)	0.86
Additional technologies [b]; n, %				
Daytime oxygen	8, 6 (95%CI 3-12)	12, 5 (95%CI 3-8)	10, 4 (95%CI 2-8)	0.71
Wheelchair	16, 13 (95%CI 8-20)	22, 8 (95%CI 6-12)	25, 11 (95%CI 7-15)	0.40
G/NG tube feeding	19, 15 (95%CI 10- 22)	40, 15 (95%CI 11-20)	40, 17 (95%CI 13-23)	0.75
V-P Shunt	3, 2 (95%CI 0.8-7)	7, 3 (95%CI 1-5)	7, 3 (95%CI 1-6)	1
Diagnostic PSG [a], median (range)				
AHI, events/hour	10 (0-197.2)	12.3 (0.4-200)	11 (0-237.9)	0.45
Mean SpO_2, %	94.7 (64-98)	95.1 (74.8-99)	94.6 (73.8-99.9)	0.34
Mean ET CO_2, mmHg	45.1 (30.4-55.8)	44.7 (31.6-72.4)	44.2 (33.9-61.5)	0.96
Mean Tc CO_2, mmHg	45.6 (34.3-65)	44.9 (35.3-99.3)	44.2 (32-72.4)	0.19

AHI, Apnea-Hypopnea index; AT, adenotonsillectomy; Cardio-Resp, cardio-respiratory (excludes UA); CNS, central nervous system; $ETCO_2$, entidal carbon dioxide; G-tube, gastrostomy tube;

MSNM, musculoskeletal and neuromuscular; NG, nasogastric; PSG, polysomnography; SpO_2, pulse oxygen saturation; $TcCO_2$, transcutaneous carbon dioxide; UA, upper airway; V-P Shunt, ventriculo-peritoneal shunt.

[a] Kruskal-Wallis test.

[b] Pearson Chi-Square test or Fisher's Exact test.

[c] Adjusted residuals for CNS were -1.3, -1.7 and 2.8 in each period respectively.

[d] Adjusted residuals for MSNM were 0.6, 2.3 and -2.8 in each period respectively.

[e] Adjusted residuals for Cardio-Resp were -0.4, -2.1 and 2.5 in each period respectively.

[f] Adjusted residuals for AT were 2.7, 1.5 and -3.8 in each period respectively.

Table 4.5. Longitudinal trends in the technology for children using long-term non-invasive ventilation.

	Jan 2005-Apr 2008 (n=127)	**May 2008-Aug 2011 (n=262)**	**Sept 2011-Dec 2014 (n=233)**	***P* Value**
Trigger for NIV [a]; n, %				
Electively with PSG	90, 71 (95%CI 62-78)	193, 74 (95%CI 68-79)	170, 73 (95%CI 67-78)	0.85
Electively without PSG	19, 15 (95%CI 10-22)	22, 8 (95%CI 6-12)	18, 8 (95%CI 5-12)	0.05
Acute illness	16, 13 (95%CI 8-19)	43, 17 (95%CI 12-21)	40, 17 (95%CI 13-23)	0.48
Other [b]	2, 1 (95%CI 0.4-6)	2, <1 (95%CI 0.2-3)	4, 2 (95%CI 0.6-4)	0.62
Location to start [a]; n, %				
Home settings	107, 84 (95% CI 77-90)	214, 82 (95%CI 77-86)	185, 79 (95%CI 74-84)	0.49
PICU	6, 5 (95%CI 2-10)	26, 10 (95%CI 7-14)	26, 12 (95%CI 0.8-16)	0.1
Ward	14, 11 (95%CI 6-18)	21, 8 (95%CI 5-12)	21, 9 (95%CI 6-13)	0.63
Interface type [a, c]; n, %				
Nasal mask [d]	75, 63 (95%CI 54-72)	109, 47 (95%CI 41-53)	156, 78 (95%CI 73-84)	**<0.001**
Full face mask [e]	43, 36 (95%CI 28-45)	120, 52 (95%CI 45-58)	40, 20 (95%CI 15-26)	**<0.001**

Other [f]	1, <1 (95%CI 0.1-5)	5, 2 (95%CI 0.9-5)	1, <1 (95%CI 0.1-3)	0.29
NIV type [a]; n, %				
CPAP	101, 80 (95%CI 72-86)	207, 79 (95%CI 74-84)	171, 73 (95%CI 67-78)	0.19
BPAP	25, 20 (95%CI 14-28)	52, 20 (95%CI 15-25)	62, 26 (95%CI 21-32)	0.17
Auto-PAP	1, <1 (95%CI 0.1-4)	3, 1 (95%CI 0.4-3)	2, <1 (95%CI 0.2-3)	>0.99
NIV settings [g]; Median (range)				
CPAP (cm H_2O) [h]	7 (4-13)	8 (4-16)	7 (4-20)	**0.03**
IPAP (cm H_2O) [i]	14 (10-22)	14 (9-22)	12 (8-22)	**0.009**
EPAP (cm H_2O)	5 (4-10)	6 (4-15)	6 (4-12)	0.42
Back-up rate [j]	18 (0-30)	20 (0-30)	15 (0-30)	**0.002**
NIV use [a]; n, %				
Night sleep	115, 91 (86-96)	227, 87 (82-91)	192, 82 (76-87)	0.09
Night sleep and naps	10, 8 (3-13)	21, 8 (4-12)	24, 10 (5-7)	0.6
Sleep and awake	2, 2 (0-4)	13, 5 (2-8)	17, 7 (2-10)	0.06

Auto-PAP, auto positive airway pressure therapy; BPAP, bilevel positive airway pressure therapy; CPAP, continuous positive airway pressure therapy; EPAP, expiratory positive airway pressure;

IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; PICU, pediatric intensive care unit; PSG, polysomnography.

[a] Pearson Chi Square or Fisher's Exact test.

[b] Other include failure to wean invasive ventilation, forced vital capacity (FVC) below 30%, and as part of palliative care treatment.

[c] Data on mask interface available in 119, 232, 199 in each epoch respectively.

[d] Adjusted residuals for nasal mask were 0.3, -6.4, and 6.3 in each period respectively.

[e] Adjusted residuals for full face mask were -0.2, 6.1 and -6.1 in each period respectively.

[f] Other interfaces: total mask, nasal pillows.

[g] Kruskal-Wallis test.

[h] Post hoc Bonferoni analysis showed differences between period 2005-2008 and 2008-2011 (adjusted p=0.03).

[l] Post hoc Bonferoni analysis showed differences between period 2008-2011 and 2011-2014 (adjusted p=0.01).

[j] Post hoc Bonferoni analysis showed differences between period 2008-2011 and 2011-2014 (adjusted p=0.002).

Table 4.6. Longitudinal trends in mortality and discontinuation rates for children using long-term non-invasive ventilation.

Reasons for discontinuation	**Jan 2005-Apr 2008 (n=127)**	**May 2008-Aug 2011 (n=262)**	**Sept 2011-Dec 2014 (n=235)**	***P* Value**
Mortality	3.4 (0.5-24.3)	39.2 (23.6-64.9)	142.1 (80.7-250.3)	**<0.001**
Family/patient decision to stop NIV	74.1 (48.8-112.5)	118.2 (88.8-157.3)	245.4 (159.9-376.3)	**<0.001**
Improvement	84.2 (56.9-124.6)	123.2 (93.1-163)	292.1 (197.4-432.3)	**<0.001**
Change to invasive ventilation	3.4 (0.5-23)	17.6 (8.4-36.9)	0	0.65
Transfer to adults	74.1 (48.8-112.5)	88 (63.2-122.6)	105.2 (54.7-202.1)	**<0.001**

Rates are expressed as number of cases per 1000 children initiated on NIV in each period per years (95% CI) and adjusted by age. NIV, non-invasive ventilation.

Table 4.7. Longitudinal trends in mortality rate for children using long-term non-invasive ventilation within each diagnostic category.

Mortality rate by diagnostic category	**Jan 2005-Apr 2008 (n=127)**	**May 2008-Aug 2011 (n=262)**	**Sept 2011-Dec 2014 (n=235)**	***P* Value**
UA	0	9.1 (2.3-36.5)	20.9 (2.9-148.1)	0.23
CNS	0	87.7 (39.4-195.1)	415 (207.6-829.9)	**<0.001**
MSNM	22.5 (3.2-159.9)	52.8 (19.8-140.7)	112.6 (15.9-799.3)	0.13
Cardio-Resp	0	152.5 (49.2-472.9)	239.3 (59.9-957)	0.09

Rates are expressed as number of cases per 1000 children initiated on NIV in each period per year (95%CI) and adjusted by age. Cardio-Resp, cardio-respiratory (excludes UA); CNS, central nervous system; MSNM, musculoskeletal and neuromuscular; NIV, non-invasive ventilation; UA, upper airway.

CHAPTER 5: LONG-TERM BENEFITS IN SLEEP, BREATHING, GROWTH AND ADHERENCE IN CHILDREN ON NON-INVASIVE VENTILATION

5.1. INTRODUCTION

This study stems from the results of our prior scoping review which identified a significant research gap in potential benefits of NIV therapies in the long-term in children, with very few included studies measuring outcomes beyond 12 months from NIV initiation and all of them being cross-sectional. That means that all the evidence on long-term NIV in children comes from comparisons at two time points, not allowing to draw conclusions about trends over time. As our clinical reality is very different with children often requiring NIV for a prolonged period, there was a clinical need to understand the potential benefits of long-term NIV therapies over time to better inform patients and families and plan for follow up. The results of this study, presented in chapter 5, are currently under review for publication.

Article in peer review: Castro-Codesal ML, Dehaan K, Bedi PK, Bendiak GN, Schmalz L, Rosychuk RJ, MacLean JE. Long-term improvements in sleep, breathing, and adherence in children on long-term non-invasive ventilation. In review by to Annals of American Thoracic Society (October 2018).

5.2. ARTICLE 4: LONG-TERM BENEFITS IN SLEEP, BREATHING AND GROWTH AND CHANGES IN ADHERENCE IN CHILDREN ON NON-INVASIVE VENTILATION

5.2.1. Abstract

Rationale

Long-term non-invasive ventilation (NIV) is a standard therapy for children with impaired sleep breathing and chronic respiratory insufficiency. Evidence of longitudinal benefits, however, is lacking.

Objectives

The aim of this study is to determine the long-term NIV efficacy, its impact on growth and changes in adherence and complication rates over time.

Methods

This multicenter retrospective longitudinal cohort study examines children started on long-term NIV over a 10-year period. Data were collected at NIV initiation, initial follow-up and most recent visit including: 1) polysomnography parameters; 2) body mass index; 3) adherence; and 4) NIV-related complications. Mixed effects models were used for longitudinal analysis.

Measurements and main results

Sufficient data were available for 429 children. Sleep parameters, apnea-hypopnea index and gas exchange improved after NIV initiation with sustained benefits over time. Changes in body mass index differed by body mass at baseline; z-score in normal weight children increased by 0.11 per year of therapy, 0.33 per year in underweight children with no change for overweight children, and a drop of 0.15 per year in obese children. The number of complications remained

low and unchanged (1.32, 95%CI 1.00 – 1.68) while adherence improved by 4% in percentage of days with use >4hr per month and 19 extra minutes per night for each year of therapy.

Conclusions

Long-term NIV is efficacious in correcting sleep and breathing parameters and demonstrated benefits in growth for underweight and obese children. Improvement in adherence and a low and stable complication rate over time suggests the burden of NIV use decreases over time.

5.2.2. Introduction

Long-term non-invasive ventilation (NIV) is considered a standard of care for children with a range of medical conditions leading to sleep related-breathing disorders and chronic respiratory insufficiency or failure. Its use has increased greatly over the last decade with a high portion of children using long-term NIV demonstrating medical complexity and surviving to adulthood.(14, 15, 17, 19-21, 26, 218) Efficacy of NIV to improve sleep and breathing during sleep in children has been established for a range of underlying conditions including obstructive sleep apnea (OSA) and other upper airway (UA) disorders, neuromuscular disorders (NMD), chronic lung diseases, abnormalities of central nervous system (CNS), and other systemic disorders.(104) However, most reports are single center, cross-sectional and with relatively short follow-up periods, making it challenging to comment on long-term efficacy. The impact of long-term NIV on growth has focused on children with obesity and has predominantly been assessed at single time points within 6 to 12 months of NIV initiation.(115, 219-221) Adherence rates and potential predictors for NIV adherence have been described in cross-sectional studies and clinical trials with short or indeterminate follow-up periods,(114, 115, 125, 126, 132, 133, 135, 222) with less data assessing adherence beyond 12 months and little investigation of complications.(128, 131, 134, 223-225)

To address these gaps, we aim to examine changes in measures of sleep, breathing and growth, and adherence and complication rates in a large multi-centered cohort of children using long-term NIV. We hypothesized that long-term NIV efficacy and benefits on sleep, breathing and body habitus will remain stable over time while adherence improve and

complication rate decrease, resulting in an overall reduction in burden of the use of long-term NIV over time.

5.2.3. Material and methods

Study Design

This multicenter regional cohort study examined all children starting long-term NIV in the province of Alberta between January 2005 and December 2014, with follow-up until June 2015. The study follows the Declaration of Helsinki and was approved by the Health Research Ethics Boards of participating institutions (HREB and CHREB).

Study Population

All children 0-18 year started on NIV and continuing use in a non-acute care setting for at least 3 months were included. NIV was defined as respiratory support delivered with an interface outside the airway, which included continuous or bi-level positive airway pressure (CPAP, BPAP).

Data Collection

Variables were collected at NIV initiation, including primary diagnoses, comorbidities, additional technologies, NIV mode (CPAP, BPAP, auto-PAP), interface type (nasal, oro-nasal, total-face), and trigger for NIV (elective, acute illness, or other reasons including failure to discontinue invasive ventilation, forced vital capacity <30% and palliative care). Primary diagnoses leading to NIV were classified as central nervous system (CNS), upper airway (UA), neuromuscular disorder (NMD), cardio and respiratory (cardio-respiratory; excludes UA), and other for unclassified conditions. Sleep and respiratory polysomnography parameters were collected from the last diagnostic study prior to starting NIV and the initial and most recent

titration studies. Data on growth, adherence and complications were collected from medical records and machine downloads at 3 times points: at NIV initiation, the first follow-up visit >3 months after starting NIV, and the most recent visit before the end of data collection. Data on body mass index (BMI) were converted to z-scores using published software.(226) Baseline BMI was classified as underweight (<-1 standard deviation (SD)), normal weight (-1SD to +1SD), overweight (>1SD to <2SD), and obese (>2SD) based on WHO standards.(227)

Statistical Analysis

Subjects were included in the analysis if they had polysomnography and growth measurements for at least two time points. Missing data were assumed to be missing at random. Mixed effects models were used to estimate changes in polysomnography parameters, BMI, adherence and complication rates over time (dependent variables). Time-varying age, sex, center and diagnostic category were included as independent variables in all models. Other covariates including number of comorbidities, number of additional technologies, baseline BMI group, NIV type, interface type, trigger for NIV initiation were tested and ultimately retained in the models if improved the model fit. The best model was selected based on the minimum Bayesian Information Criteria. Interactions between significant covariates and time were also tested. Estimates were presented as mean and 95% confidence interval (CI). Hypotheses were two-sided, and p-values were considered statistically significant at <0.05. SPSS version 24.0 (1989, 2016) was use for data analysis. Additional details of the methodology are provided in an online data supplement.

5.2.4. Results

Sufficient data for inclusion were available for 429 subjects out of 622 children started on NIV during the inclusion period. Compared to excluded subjects, included subjects were older and showed slight differences in the distribution of diagnostic categories, with more children with UA conditions (e-Table 1). The mean age at NIV initiation was 9.0±5.2 years and the most common diagnostic category was UA (Table 1). One or more comorbidities were identified in 93% of children and one or more additional technologies in 19%. Most children (71%) were overweight or obese at baseline. Time from NIV initiation to first follow-up visit was 0.7±0.6 years and to most recent follow-up visit was 2.8±1.9 years.

Sleep and Respiratory Polysomnography Parameters

There were improvements in sleep and respiratory parameters after NIV (Table 2), with increased sleep efficiency, lower arousal index, lower apnea-hypopnea index (AHI) and improved gas exchange in both the initial and most recent titration polysomnography studies (Figure 1). Increasing age was associated with lower AHI but no changes on gas exchange across polysomnography studies. In contrast, BPAP use and the presence of more comorbidities were associated with worse gas exchange but similar AHI across polysomnography studies (e-Table 2 and e-Table 3).

Growth Parameters

Changes in BMI over time differed by BMI group at baseline (Figure 2). Underweight children gained 0.44 (95%CI 0.19 – 0.69) in BMI z-score per year on NIV while normal weight children showed an increase in BMI z-score by 0.11 (95%CI 0.02 – 0.20) per year on NIV. BMI in

overweight children remained stable over time -0.10 (95%CI -0.24 – -0.05), while BMI z-score in obese children decreased by 0.15 (95% CI 0.18 – 1.24) per year on NIV.

Other than age and additional technologies, demographic and clinical covariates had no association with changes in BMI. BMI z-score decreased by 0.04 (95%CI 0.01 – 0.07) for each year of age and by 0.46 (95%CI 0.11 – 0.81) for each additional technology in use (e-Table 4). BMI change was not associated with NIV-related covariates.

NIV Adherence

Overall, NIV adherence improved over time, with a 2.8% (95%CI 0.99 – 4.53) increase in percentage of nights with NIV use >4hours per month and 19 (95%CI 8.21 – 29.85) extra minutes per night of NIV use for each year of NIV.

Increasing age was associated with a loss of 7 (95%CI 0.83 – 10.37) minutes per night of NIV use for each year of age but no changes in the percentage of nights with NIV use >4h per month (e-Table 5). A primary diagnosis of a cardio-respiratory condition was associated with a 17.23% (95%CI 0.72 – 33.74) increase in percentage of nights with NIV use >4h and 111 (95%CI 14.49 – 207.35) extra minutes per night, compared to children with UA conditions. Each NIV complication resulted in 20 (95%CI 5.61 - 33.66) fewer minutes of NIV use per night but the same percentage of nights with NIV use >4h. BPAP use was associated with 95 (95%CI 32.96 – 156.80) more minutes of NIV use per night, compared to CPAP, but no difference in percentage of nights with NIV use >4h across time. There were no differences in adherence by interface type.

Physician-Reported NIV Complications

The rate of physician-reported NIV complications remained low and stable over time, with an average of 1.32 (95%CI 1.00 – 1.68) complications per year.

Younger children had higher number of complications with a 0.03 (95%CI 0.01 – 0.06) decrease for each added year of age (e-Table 6). Other demographic and clinical covariates were not associated with changes in complication rate. While NIV type or trigger for initiation of NIV was not associated with complication rate, children using total-face masks had 1.11 (95%CI 0.07 – 2.16) more complications compared to nasal masks with no difference in the complication rate between children using oro-nasal and nasal masks.

5.2.5. Discussion

This longitudinal study provides data to support long-term benefits of NIV in children almost 3 years after NIV initiation. The results show sustained improvements in sleep, reduction of AHI, and improvements in gas exchange after adjustment for demographic, clinical, and technology-related covariates. The results also highlight that body habitus at the time of NIV initiation influences subsequent growth trends with increasing BMI z-score for underweight children and reduction in BMI z-score for obese children. Finally, NIV adherence improved over time while the number of physician-reported NIV complications remained low.

While it is clear that NIV is successful at reducing respiratory events and improving gas exchange in the short-term, the long-term benefits of NIV use in children is less well studied. For example, NIV has been shown to be beneficial for improving sleep quality, and nocturnal and diurnal gas exchange immediately after NIV initiation in children with NMD (83, 87, 228-231) but evidence beyond 12 months is limited to one randomized trial and three observational studies, all of them of small size.(157, 232-234) Large evidence supports short-term NIV efficacy in children with OSA (114, 115, 134, 166, 175, 186, 235, 236) but no studies have addressed NIV

efficacy beyond 12 months. A Cochrane review in adults and children with moderate to severe cystic fibrosis concluded that nocturnal NIV use in addition to oxygen may improve gas exchange to a greater extent than oxygen alone, based on two single-night clinical trials and a 6-week trial, but not studies have assessed benefits in the long-term.(99) The results of the current study demonstrate sustained NIV efficacy in the long-term to improve both sleep and respiratory parameters regardless of the underlying condition with small impacts of covariates on these effects.

Given the high obesity rates among children and its association with sleep-related breathing disorders, the impact of NIV treatment on body habitus is important. Several studies on childhood OSA have reported weight or BMI gain following adenotonsillectomy.(237-239) The only randomized trial of OSA children comparing early adenotonsillectomy versus a 7-month watchful waiting showed an overall small BMI increase in both groups but larger in the adenotonsillectomy group, suggesting that treatment of OSA might result in BMI gain.(238) Interestingly, subgroup analysis showed different trends by preoperative BMI, with larger increase in BMI in both underweight and normal weight children in the adenotonsillectomy group and no differences in BMI change between groups for overweight/obese children. A medical chart review including 815 children who underwent adenotonsillectomy also showed an overall increase in BMI that plateaued 12 months post-operatively. Greater gains were seen in children with baseline 1-60th weight percentiles and no gains in children with pre-operative BMI greater than 80th percentile. (240) Studies of the impact of long-term NIV on body habitus are limited to children with OSA showing stable BMI at 6-12 months follow-up.(115, 219-221) Our study is the largest to demonstrate that pre-NIV BMI is an important predictor of BMI changes following NIV

initiation. Consistent with studies of adenotonsillectomy, our results show that underweight children increase their BMI after NIV initiation. Contrary to prior evidence, our results demonstrate BMI reduction in obese children during an average follow-up of almost 3 years, highlighting the need for longer follow-up to see the full impact of NIV on body habitus. Future prospective studies including consideration for other strategies for weight management are needed to further explore the impact of long-term NIV on maintaining or restoring a healthy body habitus.

Adherence to long-term NIV therapy is a major obstacle for both children and adults. Reported adherence rate in children ranges from 21 to 87%, with some of the variation attributable to differences in definitions of adequate adherence, and mean nightly NIV use from 2.1 to 8.7 hours.(39, 114, 115, 125, 126, 132, 133, 175, 222) However, despite the long-term use of NIV, most data available in children come from cross-sectional studies within the first 6 months of therapy. Of five studies reporting NIV adherence beyond 12 months, three showed high adherence rates in over 70% of children,(134, 223, 224) consistent with our results, while two qualitative studies analyzing barriers to adherence reported adherence rate of 33-40%.(128, 131) Two single-center studies examining changes in adherence over time showed that initial use predicted later use at 6 and 12 months.(115, 224) Our study adds to these studies by reporting increasing adherence trends to an average of almost 3 years. Further, our results show differences in adherence by clinical factors such as diagnostic category, suggesting a role for distinct approaches to long-term NIV initiation for different groups of children.

Despite the fact that complications likely impact adherence, there has been little, if any, systematic study of long-term NIV-related complication rates in children. Information on a broad

range of complications has been reported anecdotally in case reports and cohorts such as mask discomfort, rhinitis, skin breakdown, conjunctivitis, tympanic membrane perforation, abdominal distension, acute gastric/bowel necrosis, supraventricular tachycardia, pneumothorax, and midface hypoplasia.(241-243) While the current study has the same limitations of prior studies using retrospective data, our results highlight that complication rates for children using long-term NIV remain low over an average follow-up of almost 3 years. Similar to other studies, it is difficult to specifically attribute complications to NIV especially when many of these children are medically complex. As complications have the potential to impact adherence with NIV as well as health and quality of life, there is need for prospective studies to better define the scope and impact of complications attributable to the use of long-term NIV.

There are limitations of our study design that must be acknowledged. In addition to the limitations of medical chart review, some children were excluded due to insufficient follow-up data on growth, with some differences in age and diagnostic category between included and excluded groups. Acknowledging that these differences might limit the interpretation of these results, children across ages and diagnostic categories were still included and the analysis was adjusted by age and diagnostic category to minimize the risk of bias. Despite having a large number of covariates, our models do not explain all the variance for outcomes so unidentified covariates may play a role in the individual trends of measured outcomes. We did run larger models including initial diagnostic polysomnographic parameters and the change in parameters from the diagnostic to the initial titration study as covariates, but this did not improve the model fit and no significant changes in the estimates. Finally, while age was included as a time-varying covariate, age alone cannot not account for developmental changes in sleep and breathing. Given

that our aim was to examine outcomes longitudinally, further work is needed to determine attribution of improvements associated with long-term NIV use.

5.2.6. Conclusions

This study confirms that long-term NIV is an efficacious therapy for children with a variety of underlying indications. The beneficial effects on sleep and respiratory parameters are sustained with positive changes in body habitus for underweight and obese children, and continued improvements in adherence over time. Overall, these results support sustained or increased benefits and reduced burden for the use of long-term NIV over time. Understanding the complications attributable to long-term NIV and how to mitigate these complications to maximize benefits is an important area for future investigation.

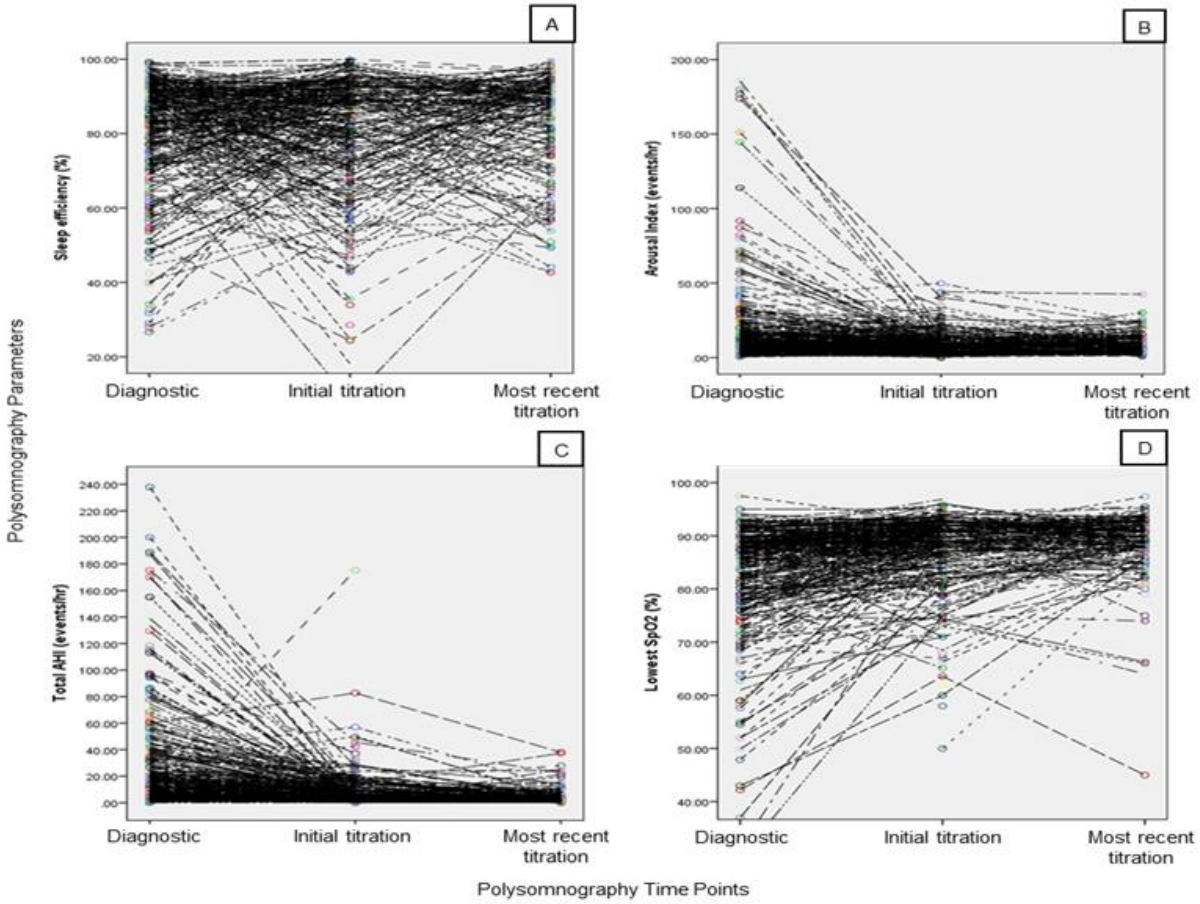

Figure 5.1. Individual trajectories of polysomnography sleep and respiratory parameters. Data from 405 children were included in the mixed models. Multivariable linear mixed models all showed significant improvements in sleep efficiency (Figure A), arousal index (Figure B), percentage of rapid eye movement (REM) sleep or infant active sleep (Figure C), and percentage of slow wave sleep or infant non-active sleep (Figure D) from the diagnostic (DIAG) to both the initial and the most recent titration polysomnography studies ($p<0.05$). Time difference between the diagnostic polysomnography and the initial titration polysomnography was 0.9 ± 1.2 years and 2.6 ± 1.9 years between the two titration polysomnography studies.

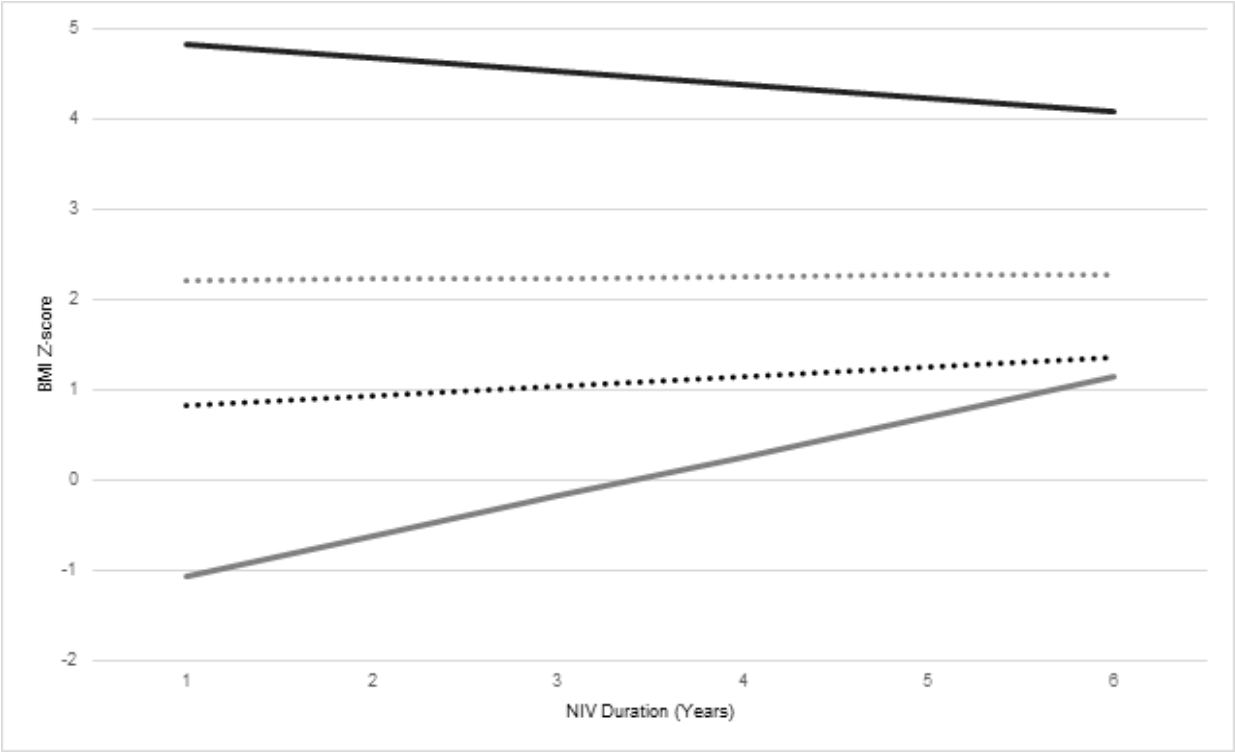

Figure 5.2. Estimated change in body mass index (BMI) z-score over time for each BMI group at baseline. Data on BMI z-scores were available in 427 children. There was a significant change in BMI z-score over time for the underweight children (Solid grey line; equation: 0.83 + 0.11 x years on NIV), normal weight (Dashed black line; equation: -1.05 + 0.44 x years on NIV) and obese groups (Solid black line; equation: 4.84 -0.15 x years on NIV). BMI z-score did not change over time in overweight children (Dashed grey line; equation: 2.22 + 0.01 x years on NIV).

Table 5.1. Comparison of demographic and clinical characteristics and NIV technology use between included and excluded subjects. * indicates $p<0.05$ for Chi-Square test or T-test comparisons.

	Included subjects Mean ± SD or N (%) (n=429)	**Excluded subjects** Mean ± SD or N (%) (n=193)
Demographic and clinical characteristics		
Age at NIV initiation, y*	9.9 ± 5.2	6.4 ± 5.2
Males	265 (62)	113 (58)
Site*		
Edmonton	211 (49)	39 (20)
Calgary	218 (51)	155 (80)
Ethnicity		
Caucasian	203 (69)	66 (69)
Aboriginal	34 (12)	11 (12)
Asian	26 (9)	14 (10)

African/ African-American	14 (5)	3 (4)
Latin American	5 (1)	1 (1)
Mixed	10 (3)	1 (3)
Diagnostic Category*		
CNS	62 (15)	45 (23)
NM	59 (14)	34 (17)
UA	277 (65)	95 (50)
Cardio-respiratory	25 (6)	14 (7)
Other	6 (1)	6 (3)
Number of comorbidities	2.5 ± 1.9	2.7 ± 2.1
Number of additional technologies	0.2 ± 0.5	0.5 ± 0.7
NIV technology		
NIV type		
CPAP	335 (78)	142 (74)
Auto-PAP	88 (21)	51 (26)
BPAP	6 (1)	0 (0)

Mask type		
Nasal mask	228 (60)	112 (66)
Oro-nasal mask	148 (39)	55 (32)
Total-face mask	4 (1)	3 (2)

AHI, apnea-hypopnea index, BMI, body mass index; CNS, central nervous system; NM, neuromuscular and musculoskeletal; NIV, non-invasive ventilation; SpO_2 oxygen saturation by pulse oximetry; TC CO_2 transcutaneous carbon dioxide; UA, upper airway.

Table 5.2. Patient characteristics at initiation of non-invasive ventilation (NIV) and NIV technology used.

Variable	Mean ± SD or N (%)
Age at NIV initiation, years	9.0 ± 5.2
Age distribution	
<2 years	59 (14)
2-5 years	51 (12)
5-12 years	17 (41)
12-18 years	142 (33)
Sex, Males: Female	265 (62): 164 (38)
Ethnicity*	
Caucasian	202 (69)
Aboriginal	34 (12)
Asian	26 (9)
African/ African-American	14 (5)
Latin American	5 (2)

Mixed	10 (3)
Diagnostic Category	
UA	276 (64)
CNS	63 (15)
NM	59 (14)
Cardio-respiratory	25 (6)
Other †	6 (<2)
Number of comorbidities	2.5 ± 1.9
Number of additional technologies	0.2 ± 0.5
Surgeries	
Adenoids and/or tonsils	218 (51)
Any major surgery ‡	144 (34)
BMI group	
Underweight (below 15th percentile)	63 (15)
Normal (15th - 85th percentiles)	60 (14)
Overweight (85th - 97th percentile)	172 (40)

Obesity (above 97th percentile)	134 (31)
NIV type	
CPAP	334 (78)
BPAP	89 (21)
Auto-PAP	6 (1)
Mask interface*	
Nasal	229 (60)
Oro-nasal	148 (39)
Total-face	4 (<1)
Trigger to NIV	
Electively (with or without polysomnography)	371 (87)
Acute illness	53 (12)
Other §	5 (1)

Auto-PAP, auto positive airway pressure; BMI, body mass index; BPAP, Bi level positive airway pressure; CNS, central nervous system; CPAP, continuous positive airway pressure; NM, neuromuscular and musculoskeletal; NIV, non-invasive ventilation; SD, standard deviation; UA, upper airway. *Data available for 291 children for ethnicity and 381 for mask interface. †

Diagnostic category 'Other' includes conditions that affect more than one diagnostic category. [‡] Any major surgery included neuro, upper airway (other than adenoids and/or tonsils surgery), cardiac, spinal, orthognathic and G-tube and/or fundoplication. [§] Other triggers for NIV initiation included force vital capacity below 30%, failure to wean invasive ventilation, palliative care purposes.

Table 5.3. Estimates of marginal means for sleep and respiratory parameters of the polysomnography studies adjusted by covariates. Data from 405 children were included. Adjusted by age at 9.5 years, sex, center, number of comorbidities at 2.5, number of additional technologies at 0.2, diagnostic category, NIV type and trigger for NIV initiation. Bold indicates statistical significance with p<0.001. Time difference between the diagnostic and the initial first titration polysomnography was 0.9 ± 1.2 years and 2.6 ± 1.9 years between the initial and most recent titration polysomnography studies.

Polysomnography Parameters	**Diagnostic Study (95%CI)**	**Initial Titration Study (95%CI)**	**Most Recent Titration Study (95%CI)**	**Pairwise Comparisons between Studies (95%CI)**	
				Diagnostic to Initial titration	**Diagnostic to FU Titration**
Sleep efficiency (%)	80.06 (75.60 – 84.51)	80.11 (75-64 – 84.57)	84.18 (79.59 – 88.76)	0.05 (-2.25 – 2.35)	**4.12 (1.54 – 6.70)**
REM (% of TST)	16.21 (13.36 – 19.05)	20.45 (17.61 – 23.3)	21.29 (18.19 – 24.39)	**4.25 (2.71 – 5.79)**	**5.08 (3.00 – 7.17)**
Slow wave sleep (% of TST)	31.67 (27.62 – 35.72)	24.34 (20.30 – 28.38)	22.92 (18.80 – 27.04)	**-7.34 (-5.08 – -9.59)**	**-8.75 (-6.32 - -11.19)**

Arousal index (events/hr.)	17.90 (14.31 – 21.49)	9.49 (6.88 – 12.10)	9.31 (6.65 – 11.98)	**-8.41 (-5.21 - -11.61)**	**-8.59 (-5.34 - -11.83)**
AHI (events/hr.)	23.29 (18.51 – 28.06)	6.53 (3.02 – 10.04)	3.79 (0.37 – 7.22)	**-16.75 (-12.35 – -21.16)**	**-19.49 (-15.23 – -23.76)**
Mean SpO_2 (%)	93.06 (92.14 – 93.98)	94.34 (93.46 – 95.22)	94.37 (93.34 – 95.40)	**1.28 (0.83 – 1.72)**	**1.31 (0.52 – 2.10)**
Minimum SpO_2 (%)	82.65 (80.41 – 84.89)	87.21 (85.09 – 89.32)	88.58 (86.40 – 90.77)	**4.56 (3.42 – 5.70)**	**5.93 (4.61 – 7.26)**
Total sleep time with SpO_2<90% (%)	15.83 (11.09 – 20.58)	10.18 (5.71 – 14.65)	9.05 (4.34 – 13.76)	**-5.65 (-2.89 – -8.41)**	**-6.78 (-3.54 – -10.03)**
Mean $TcCO_2$ (mmHg)	44.33 (42.30 – 46.37)	43.32 (41.31 – 45.34)	42.46 (40.38 – 44.53)	**-1.01 (-0.18 - -1.84)**	**-1.88 (-0.83 – -2.93)**

AHI, apnea-hypopnea index; CI, confidence interval; FU, follow up; REM, rapid eye movement; SpO_2, oxygen saturation by pulse oximetry; $TcCO_2$ transcutaneous carbon dioxide.

Table 5.4. Final multivariable linear mixed effects regression coefficients for sleep outcomes of the polysomnography (PSG). Time difference between the diagnostic polysomnography and the initial titration polysomnography was 0.9 ± 1.2 years and 2.6 ± 1.9 years between the two titration polysomnography studies. The intercept represents the average of each outcome at the diagnostic PSG. REF indicates the reference value of each covariate represented by the intercept. Clinical and technology-related covariates and the interactions between significant covariates and the three PSG time points were tested and ultimately retained in the model if improvement of model fit. Lack of data indicates exclusion from the model. Bold indicates statistical significance effects at $p<0.05$.

COVARIATES	**Sleep efficiency** **% (95%CI)**	**REM** **% of TST (95%CI)**	**Slow wave sleep** **% of TST (95%CI)**	**Arousal index** **events/hr (95%CI)**
	Multivariable	**Multivariable**	**Multivariable**	**Multivariable**
PSG type:				
Diagnostic PSG (Intercept)	**87.22** **(83.77 – 90.68)**	**14.71** **(12.93 – 16.49)**	**35.98** **(32.80 – 39.15)**	**19.37** **(16.25 – 22.50)**
Initial titration PSG	0.05 (-1.83 – 1.94)	**4.25** **(3.00 – 5.51)**	**-7.34** **(-5.49 – -9.19)**	**-8.41** **(-5.78 – -11.03)**
FU titration PSG	**4.11** **(2.00 – 6.23)**	**5.08** **(3.37 – 6.79)**	**-8.75** **(-6.75 – -10.75)**	**-8.59** **(-5.92 – -11.25)**
Demographic covariates:				

Age (years)	**-0.60** **(-0.39 – -0.81)**	**-**	**-0.53** **(-0.34 – -0.73)**	0.09 (-0.04 – 0.21)
Sex (female vs male)	0.53 (-1.62 – 2.69)	-0.18 (-1.56 – 1.20)	1.54 (-0.39 – 3.49)	0.56 (-0.68 – 1.81)
Site (Calgary vs Edmonton)	-0.09 (-2.35 – 2.18)	0.48 (-0.98 – 1.93)	**-4.02** **(-1.98 – -6.06)**	**-5.89** **(-4.58 – -7.21)**
Clinical covariates:				
Diagnostic category				
- UA	REF	REF	REF	REF
- CNS	**-3.93** **(-0.64 – -7.23)**	-0.93 (-3.02 – 1.17)	-0.96 (-3.91 – 1.99)	0.91 (-1.00 – 2.82)
- NM	**-3.72** **(-0.46 – -6.98)**	0.77 (-1.33 – 2.86)	-1.68 (-4.60 – 1.25)	-0.65 (-2.50 – 1.19)
- Cardio-Respiratory	0.58 (-4.85 – 6.00)	0.63 (-2.83 – 4.09)	**-5.33** **(-0.49 – -10.21)**	0.77 (-2.40 – 3.93)
- Other *	-1.03	0.97	2.80	-2.36

	(-10.84 – 8.78)	(-5.00 – 6.95)	(-5.73 – 11.34)	(-8.00 – 3.28)
Number of comorbidities	0.32 (-0.34 – 0.98)	0.10 (-0.32 – 0.52)	**0.64 (0.04 – 1.23)**	-0.08 (-0.45 – 0.30)
Number of additional therapies	-0.02 (-2.81 – 2.76)	0.17 (-1.61 – 1.98)	0.40 (-2.11 – 2.90)	0.19 (-1.40 – 1.79)
BMI group at baseline	-	-	-	-
NIV-related covariates:				
NIV type (BPAP vs CPAP)	**-3.33 (-0.29 – -6.37)**	0.95 (-0.99 – 2.90)	2.02 (-0.69 – 4.74)	1.51 (-0.19 – 3.22)
Interface type:				
- Nasal mask	-	-	-	-
- Oro-nasal mask	-	-	-	-
- Total-face mask	-	-	-	-
Trigger for NIV:				
- Electively at home	REF	REF	REF	REF

- Acute illness †	-2.08 (-6.13 – 1.96)	**2.97** **(0.39 – 5.54)**	**4.52** **(0.84 – 8.20)**	1.49 (-0.80 – 3.79)
- Other ‡	4.14 (-6.45 – 14.72)	-2.06 (-8.86 – 4.74)	-3.35 (-12.85 – 6.15)	-1.42 (-7.71 – 4.87)

BMI, body mass index; BPAP Bi-level positive airway pressure; CNS, central nervous system; CPAP continuous positive airway pressure; FU, follow up; NIV, non-invasive ventilation; NM, neuromuscular and musculoskeletal; PSG, polysomnography; REF, reference; REM, rapid eye movement; SE, sleep efficiency; SWS, slow wave sleep; TST, total sleep time; UA, upper airway.

* Diagnostic category 'other' included children with conditions that belong to more than one diagnostic category. † Acute illness includes admission in PICU, admission in the ward, and recurrent respiratory illnesses. ‡ Other triggers for NIV include failure to discontinue invasive ventilation, forced vital capacity <30%, palliative care and others.

Table 5.5. Final multivariable linear mixed effects regression coefficients for respiratory outcomes of the polysomnography. Time difference between the diagnostic polysomnography and the initial titration polysomnography was 0.9 ± 1.2 years and 2.6 ± 1.9 years between the two titration polysomnography studies. The intercept represents the average of each outcome at the diagnostic PSG. REF indicates the reference value of each covariate represented by the intercept. Clinical and technology-relate covariates and the interactions between significant covariates and the three PSG time points were tested and ultimately retained in the model if improvement of model fit. Lack of data indicates exclusion from the model. Bold indicates statistical significance effects at $p<0.05$.

COVARIATES	**AHI events/hr. (95%CI)**	**Mean SpO_2 % (95%CI)**	**Minimum SpO_2 % (95%CI)**	**%TST with SpO_2<90% (95%CI)**	**$TcCO_2$ mmHg (95%CI)**
	Multivariable	**Multivariable**	**Multivariable**	**Multivariable**	**Multivariable**
PSG type:					
Diagnostic PSG (Intercept)	**26.53 (22.38 – 30.69)**	**95.24 (94.51 – 95.98)**	**82.03 (80.26 – 83.81)**	**4.63 (0.98 – 8.29)**	**41.19 (39.70 – 42.68)**
Initial titration PSG	**-16.76 (-13.15 – -20.36)**	**1.28 (0.91 – 1.64)**	**4.56 (3.62 – 5.49)**	**-5.65 (-3.39 – -7.91)**	**-1.00 (-0.33 – -1.69)**

FU titration PSG	**-19.49** **(-15.99 – -22.99)**	**1.31** **(0.66 – 1.96)**	**5.93** **(4.85 – 7.02)**	**-6.78** **(-4.12 – -9.45)**	**-1.88** **(-1.01 – -2.74)**
Demographic covariates:					
Age (years)	**-0.19** **(-0.03 – -0.35)**	**-0.06** **(-0.02 – -0.11)**	**0.20** **(0.09 – 0.30)**	0.09 (-0.12 – 0.30)	0.08 (-0.01 – 0.17)
Sex (female vs male)	**-1.88** **(-0.30 – -3.45)**	0.31 (-0.13 – 0.76)	**1.10** **(0.04 – 2.15)**	-1.18 (-3.20 – 0.93)	-0.77 (-1.70 – 0.15)
Site (Calgary vs Edmonton)	-1.00 (-2.66 – 0.65)	-0.09 (-0.55 – 0.38)	**1.96** **(0.85 – 3.08)**	-0.12 (-2.35 – 2.10)	**2.74** **(1.75 – 3.73)**
Clinical covariates:					
Diagnostic category					
- UA	REF	REF	REF	REF	REF
- CNS	2.03 (-0.39 – 4.44)	0.31 (-0.37 – 0.99)	-0.89 (-2.50 – 0.71)	-0.49 (-3.71 – 2.73)	-1.19 (-2.61 – 0.24)
- NM	-0.64	0.20	1.34	-1.68	**-1.65**

	(-2.94 – 1.65)	(-0.48 – 0.88)	(-0.27 – 2.95)	(-4.85 – 1.49)	**(-0.23 – -3.09)**
- Cardio-Respiratory	-1.37 (-5.52 – 2.78)	-0.82 (-1.93 – 0.28)	0.12 (-2.57 – 2.81)	2.79 (-2.57 – 8.15)	1.15 (-1.19 – 3.44)
- Other *	-0.20 (-7.69 – 7.28)	0.98 (-0.91 – 2.88)	2.14 (-2.40 – 6.68)	-5.86 (-15.04 – (3.32)	-2.11 (-6.19 – 1.96)
Number of comorbidities	0.73 (-0.41 – 0.56)	**-0.21** **(-0.07 – -0.34)**	**-0.53** **(-0.21 – -0.85)**	**1.00** **(0.36 – 1.64)**	**0.33** **(0.05 – 0.61)**
Number of additional therapies	-0.10 (-2.10 – 1.91)	-0.27 (-0.85 – 0.30)	**-1.69** **(-0.33 – -3.06)**	1.37 (-1.38 – 4.12)	0.81 (-0.40 – 2.02)
BMI group at diagnosis	-	-	-	-	-
NIV-related covariates:					
NIV type (BPAP vs CPAP)	0.63 (-1.49 – 2.76)	**-1.05** **(-0.41 – -1.68)**	**-2.29** **(-0.80 – -3.78)**	**5.26** **(2.29 – 8.22)**	**1.44** **(0.11 – 2.78)**
Interface type					
- Nasal mask	-	**-**	**-**	**-**	**-**
- Oro-nasal mask	-	**-**	**-**	**-**	**-**

- Total-face mask	-	**-**	**-**	**-**	**-**
Trigger for NIV					
- Electively at home	REF	REF	REF	REF	REF
- Acute illness †	1.95 (-0.98 – 4.88)	-0.12 (-0.95 – 0.70)	**-3.63** **(-1.67 – -5.59)**	**5.08** **(1.17 – 8.99)**	**1.84** **(0.16 – 3.52)**
- Other ‡	-3.43 (-11.39 – 4.54)	**-2.25** **(-0.06 – -4.44)**	2.13 (-3.08 – 7.35)	**15.17** **(4.25 – 26.09)**	-0.35 (-5.37 – 4.68)

AHI, apnea-hypopnea index; BMI, body mass index; BPAP Bi-level positive airway pressure; CNS, central nervous system; CPAP continuous positive airway pressure; FU, follow up; NM, neuromuscular and musculoskeletal; PSG, polysomnography; REF, reference; SpO_2, oxygen saturation by pulse oximetry; $TcCO_2$, transcutaneous carbon dioxide level; UA, upper airway. * Diagnostic category 'other' included children with conditions that belong to more than one diagnostic category. † Acute illness includes admission in PICU, admission in the ward, and recurrent respiratory illnesses. ‡ Other triggers for NIV include failure to discontinue invasive ventilation, forced vital capacity <30%, palliative care and others.

Table 5.6. Multivariable linear mixed effects regression coefficients for BMI z-score. Final model with included parameters. The intercept represents the average BMI z-score at NIV initiation for the reference group. REF indicates the reference value of each covariate represented by the intercept. Clinical and technology-relate covariates and the interactions between significant covariates and NIV time were tested and ultimately retained in the model if improvement of model fit. Lack of data indicates exclusion from the model. Bold indicates statistical significance effects at $p<0.05$.

Covariates	**BMI z-scores**	
	Multivariable	
	Regression coefficients	**95% CI**
BMI z-score (Intercept)	**0.83**	**0.32 – 1.34**
NIV time (years)	**0.11**	**0.02 – 1.20**
Demographic covariates:		
Age (years)	**0.04**	**0.01 – 0.07**
Sex (female vs male)	-0.20	-0.50 – 0.08
Site (Calgary vs Edmonton)	**-0.31**	**-0.01 – -0.62**
Clinical covariates:		

Diagnostic category		
- UA	REF	
- CNS	0.03	-0.40 – 0.46
- NM	-0.27	-0.71 – -0.17
- Cardio-Respiratory	-0.54	-1.20 – 0.11
- Other *	0.34	-0.90 – 1.58
Number of comorbidities	-0.02	-0.10 – 0.07
Number of additional therapies	**-0.46**	**-0.11 – -0.81**
BMI group at baseline:		
- Normal weight	REF	REF
- Underweight	**-1.88**	**-1.41 – -2.36**
- Overweight	**1.39**	**0.91 – 1.87**
- Obese	**4.01**	**3.64 – 4.38**
NIV time*Normal weight	REF	REF
NIV time* Underweight	**0.33**	**0.17 – 0.50**

NIV time*Overweight	-0.10	-0.24 – 0.05
NIV time*Obese	**-0.26**	**-0.14 – -0.37**
NIV-related covariates:		
NIV type (BPAP vs CPAP)	-0.01	-0.40 – 0.38
Interface type:		
- Nasal mask	-	-
- Oro-nasal mask	-	-
- Total-face mask	-	-
Trigger for NIV:		
- Electively	REF	REF
- Acute illness †	0.55	-0.91 – 2.01
- Other ‡	0.34	-0.16 – 0.83

BMI, body mass index; BPAP, Bi-level positive airway pressure; CI, confidence interval; CNS, central nervous system; CPAP, continuous positive airway pressure; NIV non-invasive ventilation; NM, neuromuscular and musculoskeletal; REF, reference value; UA, upper airway. * Diagnostic category 'other' included children with conditions that belong to more than one diagnostic category. † Acute illness includes admission in PICU, admission in the ward, and

recurrent respiratory illnesses. ‡ Other triggers for NIV include failure to discontinue invasive ventilation, forced vital capacity <30%, palliative care and others.

Table 5.7. Multivariable linear mixed effects regression coefficients for NIV adherence data. Data on percentage of nights with NIV use >4 hours and number of hours of NIV use (days used) were available for 258 and 233 children respectively. Final model with included parameters. The intercept represents the percentage of nights with NIV use above 4 hours and the total number of hours of NIV use at NIV initiation for reference group. REF indicates the reference value of each covariate represented by the intercept. Interactions between significant covariates and NIV time were tested and ultimately not retained due to lack of improvement of model fit. Lack of data indicates exclusion from the model. Bold indicates statistical significance effects at $p<0.05$.

Covariates	**% of nights with NIV use >4hr**		**Hours of NIV use (days used)**	
	Multivariable		**Multivariable**	
	Regression coefficients	**95% CI**	**Regression coefficients**	**95% CI**
Adherence (intercept)	**63.55**	**50.96 – 76.15**	**7.27**	**6.00 – 8.53**
NIV time (years)	**2.76**	**0.99 – 4.53**	**0.32**	**0.14 – 0.50**
Demographic covariates:				
Age (years)	-0.17	-0.97 – 0.62	**-0.09**	**-0.01 – -0.17**
Sex (female vs male)	0.23	-8.39 – 7.27	0.1	-0.54 – 1.00

Site (Edmonton versus Calgary)	-5.22	-13.72 – 3.28	-0.66	-1.51 – 0.18
Clinical covariates:				
Diagnostic category				
- Upper airway	REF	REF	REF	REF
- CNS	10.55	-1.49 – 22.58	0.62	-0.55 – 1.79
- NM	-1.74	-13.31 – 9.84	0.40	-0.74 – 1.54
- Cardio-respiratory	**17.23**	**0.72 – 33.73**	**1.85**	**0.24 – 3.46**
- Other *	-18.40	-51.42 – 14.61	-0.44	-3.66 – 2.79
Number of comorbidities	-0.72	-2.97 – 1.54	-0.02	-0.24 – 0.20
Number of additional therapies	0.38	-8.35 – 9.11	-0.26	-1.11 – 0.59
Number of NIV complications	-2.04	-4.35 – 0.26	**-0.33**	**-0.09 – -0.56**
BMI group at baseline	-	-	-	-
NIV covariates:				

NIV type (BPAP vs CPAP)	9.80	-0.56 – 20.19	**1.58**	**0.55 – 2.61**
Interface type:				
- Nasal mask	REF	REF	REF	REF
- Oro-nasal mask	4.42	-3.88 – 12.72	0.49	-0.33 – 1.30
- Total-face mask	28.73	-8.86 – 66.32	2.84	-1.42 – 7.10
Trigger for NIV:				
- Electively	-	-	-	-
- Acute illness †	-	-	-	-
- Other ‡	-	-	-	-

BMI, body mass index; BPAP, Bi-level positive airway pressure; CI, confidence interval; CNS, central nervous system; CPAP, continuous positive airway pressure; NIV non-invasive ventilation; NM, neuromuscular and musculoskeletal; REF, reference value; UA, upper airway. * Diagnostic category 'other' included children with conditions that belong to more than one diagnostic category. † Acute illness includes admission in PICU, admission in the ward, and recurrent respiratory illnesses. ‡ Other triggers for NIV include failure to discontinue invasive ventilation, forced vital capacity <30%, palliative care and others.

Table 5.8. Multivariable linear mixed effects regression coefficients for number of reported NIV complications. Final model with included parameters. Data on total number of physician-reported NIV complications were available for 381 children. The intercept represents the average number of NIV physician-reported complications at NIV initiation for the reference group. REF indicates the reference value of each covariate represented by the intercept. Interactions between significant covariates and NIV time were tested and ultimately retained in the model if improved model fit. Lack of data indicates exclusion from the model. Bold indicates statistical significance effects at $p<0.05$.

Covariates	**Number of NIV physician-reported complications**	
	Multivariable	
	Regression coefficients	**95% CI**
Number of complications (intercept)	**1.32**	**1.00 - 1.68**
NIV time (years)	-0.6	-0.12 – 5.71
Demographic covariates:		
Age (years)	**-0.03**	**-0.01 – -0.06**
Sex (female vs male)	-.003	-0.22 - -0.22
Site (Edmonton versus Calgary)	0.03	-0.21 – 0.26

Clinical covariates:		
Diagnostic category		
- UA	REF	REF
- CNS	0.08	-0.25 – 0.41
- NM	-0.09	-0.41 – 0.23
- Cardio-Respiratory	-0.41	-0.90 – 0.09
- Other *	-0.18	-1.19 – -0.83
Number of comorbidities	0.06	-0.0002 – 0.13
Number of additional therapies	0.26	0.0001 – 0.52
BMI group at baseline	-	-
NIV-related covariates:		
NIV type (BPAP vs CPAP)	0.14	-0.16 – 0.44
Interface type:		
- Nasal mask	REF	REF
- Oro-nasal mask	0.13	-0.9 – 0.36

- Total-face mask	**1.11**	**0.07 – 2.16**
Trigger for NIV:		
- Electively	REF	REF
- Acute illness †	-0.01	-0.38 – 0.36
- Other ‡	-1.00	-2.15 – 0.15

BMI, body mass index; BPAP, Bi-level positive airway pressure; CI, confidence interval; CNS, central nervous system; CPAP, continuous positive airway pressure; NIV non-invasive ventilation; NM, neuromuscular and musculoskeletal; REF, reference value; UA, upper airway. * Diagnostic category 'other' included children with conditions that belong to more than one diagnostic category. † Acute illness includes admission in PICU, admission in the ward, and recurrent respiratory illnesses. ‡ Other triggers for NIV include failure to discontinue invasive ventilation, forced vital capacity <30%, palliative care and others.

CAPÍTULO 6: RESUMEN, CONCLUSIONES Y DIRECCIONES FUTURAS (Versión en castellano)

Los resultados recopilados en esta tesis proporcionan un resumen completo de la evidencia científica disponible en la actualidad y respaldan el uso de la ventilación no invasiva (VNI) prolongada en niños y niñas con una gran variedad de patologías. El análisis poblacional multicéntrico de nuestra cohorte regional durante una década describe los cambios en las características clínicas, uso de la tecnología y resultados clínicos a largo plazo. Nuestro estudio longitudinal analiza los cambios en variables clínicas relevantes en este grupo de pacientes, incluyendo parámetros de sueño, respiración durante el sueño y crecimiento, así como cambios en la adhesión al tratamiento y la tasa de complicaciones relacionadas con VNI. En conjunto, los resultados de esta tesis proporcionan el primer resumen sistemático de la evidencia actual en el uso de VNI prolongada en pediatría y abordan algunas de las lagunas identificadas en la evidencia científica, con información relevante que puede contribuir a mejorar el enfoque clínico hacia este grupo de pacientes.

6.1. RESUMEN Y CONCLUSIONES

Nuestra revisión sistemática exploratoria resume la evidencia científica en el campo de la VNI prolongada en pediatría. De los resultados de este trabajo, surge la identificación de múltiples términos que se refieren a terapias de VNI, lo que genera dificultades en la búsqueda de información en la literatura científica y confusión con respecto a qué terapias de asistencia respiratoria se consideran VNI. Este hecho apoya la necesidad de un lenguaje unificado para describir terapias de VNI y facilitar el trabajo de profesionales tanto en el ámbito clínico como el de la investigación. Una terminología común permitiría la fácil identificación de terapias

respiratorias de presión positiva administradas a través de una interfase (CPAP, presión positiva continua, o BPAP, presión positiva de dos niveles) y diferenciarlas de aquellas administradas a través de tubo endotraqueal o traqueostomía (CPAP invasivo o BPAP). Además, una terminología común facilitará la discusión sobre la posible cobertura sanitaria para ambas terapias, evitando inequidades en la financiación pública de los diferentes tipos de VNI. Otro resultado relevante de nuestra revisión sistemática fue la evidencia de uso de VNI en niños y niñas con una gran variedad de patologías, aunque la mayoría de los estudios incluidos se reducen a pacientes con dos patologías: apnea obstructiva del sueño y atrofia muscular espinal. Por tanto, existe la necesidad de realizar más esfuerzos para recopilar datos sobre muchas otras poblaciones pediátricas que actualmente utilizan VNI prolongada. Muy notablemente, esta revisión demostró la baja calidad metodológica de la mayoría de los estudios disponibles, lo que genera dificultades para generalizar conclusiones, destacando la urgente necesidad de estudios con una metodología más rigurosa. El resumen de los resultados de los estudios incluidos en nuestra revisión sistemática exploratoria reveló un uso recurrente de parámetros procedentes de estudios polisomnográficos del sueño, así como otros parámetros respiratorios no estandarizados para inferir cambios en morbilidad respiratoria. Sin embargo, estos parámetros podrían no representar las preocupaciones reales de niños y niñas con VNI y sus familias. Se han realizado escasos esfuerzos en el desarrollo de estrategias que identifiquen variables clínicas de interés para pacientes y familias y, por consiguiente, existe una laguna en el conocimiento en aspectos tan importantes como la calidad de vida, la carga del tratamiento o la resolución de síntomas no respiratorios tales como cambios beneficiosos en el sueño, desarrollo neurocognitivo, comportamiento o estado de ánimo. Por lo tanto, es necesario el

desarrollo de estrategias que ayuden a identificar aspectos relevantes para el paciente y un mayor esfuerzo para estandarizar parámetros respiratorios y no respiratorios más allá de datos procedentes de estudios del sueño. Finalmente, en esta tesis se recopilan publicaciones que aportan mucha información sobre otras variables no analizadas en profundidad en este trabajo pero que serían dignas de evaluar en el futuro mediante revisión sistemática y metaanálisis adicional. Por ejemplo, el metaanálisis de las tasas de adhesión a la VNI en pediatría y revisión sistemática de los factores que pueden tener impacto en la adhesión al tratamiento pueden ser de gran utilidad y directamente aplicables a nuestra práctica clínica. Se pueden abordar muchas otras cuestiones con los datos encontrados en la literatura existente. Por ejemplo, el impacto de VNI prolongada en la supervivencia y síntomas respiratorios de pacientes con enfermedades neuromusculares no ha sido estudiado con anterioridad. Otros ejemplos podrían ser la revisión sistemática y metaanálisis del impacto de la VNI prolongada en el hábito corporal y otros parámetros metabólicos en pacientes con obesidad y OSA, o el uso y resultados de la VNI prolongada en lactantes.

El análisis poblacional de tendencias ha proporcionado información relevante sobre los cambios acontecidos en la cohorte de niños y niñas con VNI prolongada durante la última década. La incidencia y prevalencia del uso de VNI prolongada ha aumentado significativamente en el tiempo, lo que probablemente refleja cambios en la supervivencia de niños y niñas con enfermedades críticas, mejoras en la tecnología que permiten mayor accesibilidad y flexibilidad en el uso de VNI en pediatría, y un mayor conocimiento sobre las posibles indicaciones de la VNI prolongada entre profesionales sanitarios. Esta tendencia ha puesto de relieve la necesidad de planes estratégicos, no solo para el cuidado de una población pediátrica en aumento que

utiliza VNI prolongada, sino también para la prestación de servicios de atención médica en adultos, dada la alta supervivencia y probabilidad de transición a servicios especializados de adultos. También ha habido un cambio en las indicaciones de VNI prolongada en pediatría, con una mayor proporción de niños y niñas con enfermedades neurológicas y cardiorrespiratorias que iniciaron VNI prolongada. Sin embargo, este cambio explica el incremento en la mortalidad global de la población pediátrica en tratamiento con VNI prolongada. Estos datos nos permitirán establecer expectativas más realistas en el uso de la VNI y brindar mejor asesoramiento clínico a las familias en función de la patología subyacente. No obstante, reconocemos que pueden existir otros beneficios de la VNI prolongada más allá de la supervivencia, como se demuestra en nuestro estudio longitudinal. Dados los resultados del estudio poblacional, destacamos la necesidad de continuar el seguimiento prospectivo de datos en esta cohorte pediátrica, más allá del análisis de la supervivencia, para poder definir otros posibles beneficios y riesgos del uso de VNI prolongada en pediatría. Finalmente, este trabajo demuestra el alto nivel de complejidad médica de pacientes pediátricos que utilizan VNI prolongada. Aunque nuestro estudio no demostró un aumento en el tiempo del grado de complejidad (medida como numero de comorbilidades y numero de terapias adicionales a la VNI) ni tampoco de la severidad de la insuficiencia respiratoria que explique el exponencial aumento de la tasa de mortalidad, quizás estos datos sugieren que el uso de VNI prolongada en sí puede ser un indicador de complejidad médica. Nos damos cuenta de que necesitamos estudios adicionales que evalúen los componentes de complejidad médica, incluido el uso de servicios médicos o el impacto emocional, social y económico para las familias, ya que esto nos ayudará a planificar los recursos necesarios y una adecuada atención médica, así como a

establecer estándares para el uso de la VNI prolongada en pediatría. Además, la aplicación de marcos de complejidad médica anteriormente descritos a futuras investigaciones puede ser útil para ayudar a diferenciar las necesidades de atención, resultados esperados y anticipar la evolución clínica, incluida la supervivencia, de individuos con y sin complejidad médica.

Nuestro estudio final analiza los cambios longitudinales en nuestra cohorte pediátrica en tratamiento con VNI prolongada, y demuestra un beneficio en el crecimiento de niños y niñas con bajo peso u obesidad. Este estudio añade conocimiento sobre la interrelación entre el sueño, el hábito corporal y el crecimiento, y sugiere que el tratamiento con VNI prolongada de trastornos respiratorios relacionados con el sueño o insuficiencia respiratoria podría contribuir a optimizar el crecimiento en subpoblaciones pediátricas de bajo peso o con obesidad. En particular, la caída en el índice de masa corporal en niños y niñas con obesidad que usan VNI prolongada es alentadora, ya que contradice estudios previos de corta duración que no demostraron dicho beneficio, así como estudios en adultos con apnea obstructiva del sueño que demostraron un aumento leve de peso entre los 3 y 12 meses después de iniciar tratamiento con VNI. Se necesitan, de hecho, estudios prospectivos adicionales en pacientes pediátricos con sobrepeso/ obesidad que evalúen el efecto en el crecimiento y otros parámetros metabólicos de la VNI prolongada en solitario o en combinación con otras terapias médicas y cambios en el estilo de vida. Finalmente, este estudio documentó una alta adhesión al tratamiento de VNI en nuestra cohorte, con mejoría a lo largo del tiempo, y una tasa baja de complicaciones que permaneció estable. Esta información es alentadora para profesionales sanitarios a cargo de niños y niñas con VNI prolongada, ya que refuerza la necesidad de una atención médica especializada y seguimiento cercano que mejoren la adhesión al tratamiento y

minimicen las complicaciones. En otras palabras, estos datos demuestran que los beneficios de la VNI prolongada en sueño, respiración y para algunos subgrupos crecimiento se mantienen, mientras que la carga del tratamiento para las familias se reduce en el tiempo. El seguimiento de datos prospectivos sobre la eficacia de diferentes intervenciones que ayuden a mejorar y mantener la adhesión al tratamiento y que reduzcan las complicaciones es, de hecho, el próximo paso en la agenda de investigación.

6.2. FUTURAS ACTUACIONES

1. **Modificación de MeSH (Medical Subject Headings, en sus términos en inglés) para indexar artículos en PubMed.** Dado el uso problemático de múltiples términos que se refieren a terapias de VNI y la falta de acuerdo sobre la inclusión de CPAP y BPAP en el marco de la VNI, proponemos el uso de un único termino que refleje ambas terapias y facilite el trabajo de profesionales clínicos e investigadores. Para llevar a cabo esta tarea, hemos planificado contactar con la National Library of Medicine (NLM, por sus siglas en inglés) que controla el diccionario de términos utilizados para la indexación de artículos en PubMed y solicitar una revisión del término MeSH 'NIV' (non-invasive ventilation, en sus términos en inglés) para incluir tanto CPAP como BPAP y abogar por evitar el uso de otros términos. Eso simplificará la indexación de artículos en PubMed y, por tanto, la búsqueda de literatura en esta área de investigación.
2. **Esfuerzos adicionales para desarrollar registros de poblaciones pediátricas que utilizan VNI prolongada y diseñar estudios multicéntricos con alta calidad metodológica.** Hemos planeado continuar la recopilación de datos de nuestra cohorte regional de niños y niñas que usan VNI prolongada con información prospectiva, así como la

expansión de nuestro registro a centros terciarios de todo Canadá. Para llevar a cabo esta tarea, contamos con nuestra base de datos REDCap, una herramienta útil para recopilar información médica de forma segura, dado su acceso es online y por tanto potencialmente accesible en cualquier lugar. Además, este modelo podría trasladarse a otros centros de ámbito nacional o internacional. Esperamos que esta base de datos multicéntrica de gran tamaño permita no solo el desarrollo de estudios multicéntricos robustos que continúen llenando los vacíos identificados a través de este trabajo de tesis, sino también futuros análisis de subgrupos sobre el impacto de la VNI en subpoblaciones pediátricas actualmente menos estudiadas. Por ejemplo, análisis adiciones en pacientes con trisomía 21, parálisis cerebral, malformaciones craneofaciales, enfermedades neuromusculares, enfermedades pulmonares crónicas o patologías cardíacas permitirían un estudio detallado de las expectativas clínicas y pronóstico en estos grupos.

3. **Estrategias para la identificación de resultados potencialmente relevantes para pacientes que usan VNI y sus familias.** En un futuro, nos gustaría desarrollar métodos cualitativos para que la participación de niños y niñas que usan VNI y sus familias nos ayude a priorizar parámetros y variables de interés, y quizás el desarrollo del análisis de nuevos parámetros con una clara orientación hacia el interés del paciente. Las entrevistas y grupos de discusión pueden ser un primer paso útil en la identificación de qué aspectos de la VNI son relevantes para las familias, así como otros aspectos que afecten a la calidad de vida del niño/a y su familia, supongan una carga de tratamiento o sean barreras en la adhesión al tratamiento con VNI. Posteriormente, se pueden

desarrollar encuestas que ayuden a priorizar la evaluación y análisis de dichos parámetros y variables según la relevancia que tenga para pacientes y sus familias y, finalmente, elaborar y validar cuestionarios con toda esta información. Esto añadiría nuevas herramientas de gran utilidad para la investigación prospectiva futura.

4. **Análisis adicional de la literatura existente.** Como resultado de este trabajo, se identificó suficiente literatura para llevar a cabo una revisión sistemática y metaanálisis sobre el uso de la VNI en lactantes y sus resultados, que ya ha sido publicado. Este trabajo resaltó el hecho de que los resultados clínicos de la VNI prolongada en el grupo de lactantes presentan diferencias claras a largo plazo según la patología subyacente. Actualmente, nuestro grupo está realizando dos revisiones sistemáticas adicionales para responder las siguientes preguntas: 1) ¿Cuáles son los beneficios de la VNI prolongada en niños y niñas con enfermedades neuromusculares y qué factores pueden afectar dichos beneficios? 2) ¿Qué parámetros se utilizan en pediatría para evaluar la adhesión al tratamiento con VNI y qué factores afectan dicha adhesión al tratamiento con la VNI prolongada en pediatría? Por último, hemos incorporado a nuestra agenda de investigación futura una revisión sistemática sobre el uso de VNI prolongada en niños y niñas con trastornos de la respiración durante el sueño y sobrepeso u obesidad y sus posibles beneficios en el sueño, respiración, hábito corporal y crecimiento, así como otros parámetros metabólicos previamente descritos como presión arterial, perfil glicémico o glucosa. Teniendo en cuenta los altos índices de obesidad en las poblaciones pediátricas actuales a nivel mundial, los posibles resultados de esta revisión sistemática podrían ser de gran relevancia clínica. Finalmente, hemos planeado una revisión de los

diferentes tipos de interfase utilizados en poblaciones pediátricas que requieren VNI prolongada, así como su impacto en eficacia, adhesión al tratamiento y complicaciones de la terapia.

5. **Análisis adicional de los datos retrospectivos**. Nos han surgido muchas otras preguntas durante la colección y el análisis de los datos retrospectivos. Por ejemplo, hemos analizado las diferencias en el uso y resultados de la VNI entre lactantes y niños mayores de dos años en un estudio de casos y controles, cuyos resultados han sido publicados recientemente. Otros posibles estudios surgidos de nuestros datos retrospectivos incluyen una descripción de la distribución geográfica de pacientes que requieren VNI prolongada en la provincia, y el impacto de la distancia entre sus domicilios y los centros de atención sanitaria especializada. Los resultados de este proyecto permitirán identificar posibles barreras geográficas para una atención óptima de este grupo de pacientes, y asignar recursos a aquellos/as con difícil acceso a la atención médica especializada. Además, hemos planeado un análisis de posibles factores que afecten los resultados a largo plazo de la VNI prolongada, como por ejemplo la interrupción de VNI debido a la mejora de la enfermedad subyacente, la decisión de paciente/familia de suspender la VNI, el cambio a ventilación invasiva y el fallecimiento. La posible identificación de variables demográficas, clínicas o relacionadas con la tecnología que podrían tener un impacto en dichos resultados tendría una aplicación directa en la práctica clínica.

6.3. CONCLUSIÓN FINAL

Esta tesis representa un trabajo de investigación extenso enfocado en ampliar el conocimiento del uso de VNI en pediatría. Sus resultados ponen de manifiesto importantes lagunas del conocimiento en la literatura disponible y, que, en parte, los estudios incluidos en esta tesis pretenden responder. Este trabajo demuestra el aumento continuo del uso de VNI prolongada en múltiples subpoblaciones pediátricas, así como demuestran beneficios sostenidos de la VNI a largo plazo en variables clínicas relevantes como el sueño, la respiración y el crecimiento. En definitiva, estos resultados no solo han contribuido a mejorar el cuidado de niños y niñas que requieren VNI si no también han generado nuevas ideas de investigación que nos estimulan a seguir trabajando por ampliar nuestro conocimiento en este tema.

CHAPTER 6: SUMMARY, CONCLUSIONS AND FUTURE DIRECTIONS (English version)

The results gathered in this thesis provide a comprehensive summary of evidence currently available to support the use of long-term NIV in children with a large variety of conditions. The analysis of our data from a regional multicenter cohort describes the changes in patient's characteristics, technology use and long-term outcomes over a decade and examines relevant longitudinal outcomes of these children. Overall, the results of this thesis provide the first systematic summary of current evidence and begins to address gaps in that evidence including important information that will inform our clinical approach to children requiring long-term NIV under our care.

6.1. SUMMARY AND CONCLUSIONS

Our scoping review has summarized prior research work in the field of long-term NIV in children. The first piece of data stemming from this work was the identification of multiple terms referring to NIV therapies, which resulted in difficulties finding information in the literature and confusion about which therapies are considered NIV. This fact supports the need for a unified language to describe NIV therapies and facilitate the work for clinicians and researchers. A common terminology will allow an easier distinction between breathing support therapies administered through a mask (CPAP or BPAP) and those administered through a tracheal tube (invasive CPAP or bi-level ventilation). In addition, a common terminology will facilitate further advocacy for public health coverage for both CPAP and BPAP and avoid inequities in funding based on the NIV type. The scoping review demonstrated evidence of NIV

use in children with a great variety of underlying conditions. However, the majority of the studies referred to the same two pediatric populations, children with OSA and children with SMA. A logical conclusion of this work is the need for further efforts to gather data on many other pediatric populations currently using long-term NIV. Remarkably, this review demonstrated the low methodological quality of most available studies and subsequent difficulties to generalize conclusions and highlighted the urgent need for studies with more rigorous methodology. The summary of the outcomes reported in the literature revealed a recurrent use of parameters from sleep studies and non-standardized respiratory outcomes to assess the impact of long-term NIV in children, which might not represent the symptoms and worries of children using NIV and their families. In contrast, there is a paucity of studies using more patient-oriented outcomes such us aspects related to quality of life, treatment burden or resolution of non-respiratory symptoms including changes in sleep, neurocognitive outcomes, behavior or mood. Therefore, it is indeed needed the development of strategies that help identify patient-oriented outcomes and further work to standardize respiratory and non-respiratory outcomes beyond data from sleep studies. Finally, relevant research questions can be answered through further systematic review and meta-analysis of the included studies in our scoping review. For instance, meta-analysis of adherence rates in children using NIV and systematic review of factors that may impact adherence will be relevant and directly applicable to our clinical practice. Many other questions can be addressed with the existing literature and should be incorporated to a future research agenda such as the respiratory improvement and survival in children with NMD, improvement in sleep, breathing, body habitus and metabolic

outcomes in children with OSA and obesity, or long-term outcomes in infants requiring long-term NIV.

Our trend analysis has provided relevant information regarding changes in the cohort of children receiving long-term NIV over the last decade. The number of children started on long-term NIV has increased over time, likely reflecting changes in survival of children with critical illness, improvements in technology and greater awareness among physicians about the use of long-term NIV therapies. This trend has highlighted the need for strategic plans not only for the care of an increasing pediatric population using long-term NIV but for provision of adult healthcare services, given the high survival and likelihood of transition into adulthood. There has also been a shift in the indications for long-term NIV in children, with a larger proportion of children with neurological and cardio-respiratory conditions starting long-term NIV over time. This change, however, accounts for a rise in the overall mortality rate over time. This data will allow us to set more realistic expectations for the use of NIV and provide better counselling to families in accordance to their child's underlying condition. We recognize that it may be benefits from long-term NIV other than survival, as further demonstrated in our longitudinal study. Further prospective tracking with systematic collection of outcomes beyond survival are, in fact, needed to better define the benefits and risks for the use of long-term NIV in children. Finally, we demonstrated a high but stable level of medical complexity in children using long-term NIV, suggesting that the use of long-term NIV itself may indicate high medical complexity. We realize that we need additional understanding of the components of medical complexity, including healthcare usage and emotional, social and financial impact for families, as this will

help us to inform the care and resources needed and set standards for the use of long-term NIV in children. In addition, the application of previously described frameworks of medical complexity to future research in children using long-term NIV may be useful to differentiate both needs for care, relevant outcomes, and anticipated trajectories including survival for those with and without medical complexity.

Our final study of the longitudinal outcomes of long-term NIV demonstrates a benefit in growth of underweight and obese children. This study adds knowledge in the interrelation between sleep, body habitus and growth, and suggests that the treatment of sleep-related breathing disorders or respiratory insufficiency with NIV might contribute to optimize growth in underweight and obese children. In particular, the drop in BMI in obese children started on long-term NIV is encouraging as it contradicts prior studies of shorter duration showing no changes in BMI as well as studies in adults with OSA that demonstrated weight gain at 3 to 12 months from NIV initiation. Further prospective studies in overweight/obese children assessing the long-term effect of NIV alone or in combination with other medical therapies and lifestyle changes in growth and metabolic outcomes are in fact needed. Finally, this study documented high adherence to NIV with improvement in adherence over time and a stable low rate of complications. This information is encouraging to continue providing specialized health care and close monitoring of children on long-term NIV to maximize adherence and minimize the chance of complications. In other words, the benefits of NIV in sleep, breathing and for some subgroups in growth seems to maintain time while the treatment burden for the families is reduced over time. Further prospective data on the efficacy of different interventions to

improve and maintain adherence and reduce complications are, in fact, the next step in the research agenda.

6.2. FUTURE DIRECTIONS

1. **Modification of MeSH (Medical Subject Headings) for indexing articles for PubMed.** Given the problematic use of multiple terms to refer to NIV and lack of agreement to include both CPAP and BPAP therapies under the NIV umbrella, we are convinced that further terminology convention is necessary to facilitate the work of clinicians and researchers. To undertake this task, we will reach the National Library of Medicine, which controls vocabulary thesaurus to convey terms used among researchers and index articles in PubMed. We have planned to request a revision of the MeSH term NIV to include both CPAP and BPAP therapies under this term and advocate for the use of the term NIV and the avoidance of other terms. That will simplify the indexing of articles in PubMed and literature search on this topic.

2. **Further efforts to develop large registries of children using long-term NIV and multicenter high-quality studies.** We have planned for further collection of prospective data on our regional cohort of children using NIV and expand the data collection to tertiary centers across Canada. To undertake this task, we count on our redcap database, which will be a useful tool to securely collect prospective information anywhere, as it can be accessed online. Furthermore, this model can be useful for future registries at international level. This multicenter database with a large sample size will not only allow the development of robust multicenter studies to continue filling the gaps identified through

this thesis work but also undertake further subgroup analysis of NIV outcomes in a variety of pediatric populations less described in the current literature. Infants and children with trisomy 21, cerebral palsy, cranio-facial abnormalities, NMD, chronic lung diseases or cardiac conditions are some examples.

3. **Strategies for identification of patient-oriented outcomes.** Looking forward, we would like to develop qualitative methods for engagement of children using NIV and their caregivers in the prioritization of outcomes and maybe development of new patient-oriented standardized outcomes. Interviews and focus groups to discuss which aspects of NIV impact their quality of life, add treatment burden or are barriers for NIV adherence will be a first step in the identification of relevant outcomes. Surveys can be used to prioritize currently used outcomes based on patients' interests. Finally, the development of questionnaires with patient-oriented outcomes and further validation to standardize measures will be incorporated into our prospective research work.

4. **More detail analysis of existing literature.** Stemming from this work, we identified enough literature to undertake a systematic review and meta-analysis to assess the use and outcomes of NIV in infants, which has already been published. This work highlighted the fact that infants are a distinct group of children with clear differences in NIV outcomes by underlying condition. Two more systematic reviews are currently underway to answer the following questions: 1) What outcomes are improved with the use of long-term NIV in children with NMD and which factors may impact outcomes? 2) What are the measurements used to assess NIV adherence in children and what factors impact

adherence to long-term NIV in children? One more systematic review on the assessment of changes in sleep, breathing, growth and metabolic outcomes such as blood pressure, lipid profile and glucose levels in children with OSA and obesity is on our future research agenda. Considering the current high rates of obesity among children worldwide, the potential findings of this systematic review could be of great relevance. Finally, we have planned for a review of the different interface types used in children requiring long-term NIV and their impact on NIV efficacy, adherence and complications.

5. **Further analysis of retrospective data.** Many other research questions have come from our large retrospective data collection. We have analyzed differences in NIV technology use and outcomes of infants using long-term NIV compared to older children in a case-control study and the results have been recently published. We also have ongoing plans to describe the geographical distribution of children requiring long-term NIV in the province and the impact of the distance between their homes and specialized NIV clinics. The results of this project will allow stakeholders to identify potential geographical barriers for optimal care, and better allocate resources for children with difficult access to the specialized healthcare. Further, we have planned an analysis of predictors for long-term outcomes including NIV discontinuation due to improvement of underlying condition, patient/family decision to stop NIV, change to invasive ventilation and death. The identification of demographic, clinical and technology-related parameters that might impact those outcomes will have a direct application in the clinical practice, not only for prognostic purposes but also to develop strategies to prevent potential adverse outcomes.

6.3. FINAL CONCLUSION

This thesis represents a large body of work focused on understanding the use of long-term NIV in children. The results highlight important gaps in knowledge, a growing and expanding trend of long-term NIV use, and benefit for relevant outcomes such us sleep, breathing and growth. While these results will contribute to improving the care of children using long-term NIV, they have also generated new ideas and questions to stimulate further study.

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